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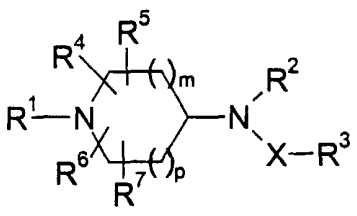
(54) Title: PHARMACEUTICALLY ACTIVE PIPERIDINE DERIVATIVES, IN PARTICULAR AS MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY



(I)

(57) Abstract: Compounds of formula (I), compositions comprising them, processes for preparing them and their use in medical therapy (for example modulating CCR5 receptor activity in a warm blooded animal).

PHARMACEUTICALLY ACTIVE PIPERIDINE DERIVATIVES, IN PARTICULAR AS MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY

The present invention relates to heterocyclic derivatives having pharmaceutical activity, to processes for preparing such derivatives, to pharmaceutical compositions comprising such derivatives and to the use of such derivatives as active therapeutic agents.

Pharmaceutically active piperidine derivatives are disclosed in EP-A1-1013276, WO00/08013, WO99/38514 and WO99/04794.

Chemokines are chemotactic cytokines that are released by a wide variety of cells to attract macrophages, T cells, eosinophils, basophils and neutrophils to sites of inflammation and also play a rôle in the maturation of cells of the immune system. Chemokines play an important role in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved four cysteine motif. The chemokine superfamily can be divided into two main groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C, or α) and Cys-Cys (C-C, or β) families. These are distinguished on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues and sequence similarity.

The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils such as human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1α and 1β (MIP-1α and MIP-1β).

Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3 and CXCR4. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

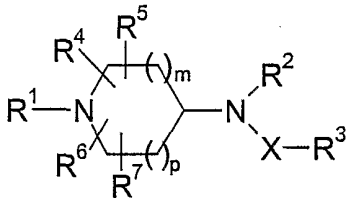
The CCR5 receptor is expressed on T-lymphocytes, monocytes, macrophages, dendritic cells, microglia and other cell types. These detect and respond to several

chemokines, principally "regulated on activation normal T-cell expressed and secreted" (RANTES), macrophage inflammatory proteins (MIP) MIP-1a and MIP-1b and monocyte chemoattractant protein-2 (MCP-2).

This results in the recruitment of cells of the immune system to sites of disease. In many diseases it is the cells expressing CCR5 which contribute, directly or indirectly, to tissue damage. Consequently, inhibiting the recruitment of these cells is beneficial in a wide range of diseases.

CCR5 is also a co-receptor for HIV-1 and other viruses, allowing these viruses to enter cells. Blocking the receptor with a CCR5 antagonist or inducing receptor internalisation with a CCR5 agonist protects cells from viral infection.

The present invention provides a compound of formula (I):



(I)

wherein:

R^1 is C_{1-6} alkyl , C_{3-7} cycloalkyl, C_{3-8} alkenyl or C_{3-8} alkynyl, each optionally substituted with one or more of: halo, hydroxy, cyano, nitro, C_{3-7} cycloalkyl, NR^8R^9, $C(O)R^{10}$, $NR^{13}C(O)R^{14}$, $C(O)NR^{17}R^{18}$, $NR^{19}C(O)NR^{20}R^{21}$, $S(O)_nR^{22}$, C_{1-6} alkoxy (itself optionally substituted by heterocyclyl or $C(O)NR^{23}R^{24}$), heterocyclyl, heterocyclyloxy, aryl, aryloxy, heteroaryl or heteroaryloxy;

R^2 is hydrogen, C_{1-8} alkyl, C_{3-8} alkenyl, C_{3-8} alkynyl, C_{3-7} cycloalkyl, aryl, heteroaryl, heterocyclyl, aryl(C_{1-4})alkyl, heteroaryl(C_{1-4})alkyl or heterocyclyl(C_{1-4})alkyl;

R^3 is C_{1-8} alkyl, C_{2-8} alkenyl, $NR^{45}R^{46}$, C_{2-8} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(C_{1-4})alkyl, heteroaryl(C_{1-4})alkyl or heterocyclyl(C_{1-4})alkyl;

R^{46} is C_{1-8} alkyl, C_{3-8} alkenyl, C_{3-8} alkynyl, C_{3-7} cycloalkyl, aryl, heteroaryl, heterocyclyl, aryl(C_{1-4})alkyl, heteroaryl(C_{1-4})alkyl or heterocyclyl(C_{1-4})alkyl;

wherein the groups of R^2, R^3 and R^{46}, and the heterocyclyl, aryl and heteroaryl moieties of R^1, are independently optionally substituted by one or more of halo, cyano, nitro, hydroxy, $S(O)_qR^{25}$, $OC(O)NR^{26}R^{27}$, $NR^{28}R^{29}$, $NR^{30}C(O)R^{31}$, $NR^{32}C(O)NR^{33}R^{34}$, $S(O)_2NR^{35}R^{36}$, $NR^{37}S(O)_2R^{38}$, $C(O)NR^{39}R^{40}$, $C(O)R^{41}$, CO_2R^{42}, $NR^{43}CO_2R^{44}$, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, phenyl, phenyl(C_{1-4})alkyl, phenoxy, phenylthio,

phenyl(C_{1-4})alkoxy, heteroaryl, heteroaryl(C_{1-4})alkyl, heteroaryloxy or heteroaryl(C_{1-4})alkoxy; wherein any of the immediately foregoing phenyl and heteroaryl moieties are optionally substituted with halo, hydroxy, nitro, $S(O)_kC_{1-4}$ alkyl, $S(O)_2NH_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3; the C_{3-7} cycloalkyl, aryl, heteroaryl and heterocyclyl moieties of R^1, R^2 and R^3 being additionally optionally substituted with C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl or C_{1-6} alkoxy(C_{1-6})alkyl;

R^4, R^5, R^6 and R^7 are, independently, hydrogen, C_{1-6} alkyl {optionally substituted by halo, cyano, hydroxy, C_{1-4} alkoxy, OCF_3, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $NHC(O)(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$C(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$S(O)_2(C_{1-4}$ alkyl), $CO_2(C_{1-4}$ alkyl), $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, $C(O)NH_2$, CO_2H, $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, heterocyclyl or C(O)(heterocyclyl)}, $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, $C(O)(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl) or C(O)(heterocyclyl); or two of R^4, R^5, R^6 and R^7 can join to form, together with the ring to which they are attached, a bicyclic ring system; or two of R^4, R^5, R^6 and R^7 can form an endocyclic bond (thereby resulting in an unsaturated ring system);

X is C(O), $S(O)_2$, C(O)C(O), a direct bond or $C(O)C(O)NR^{47}$;

k, m, n, p and q are, independently, 0, 1 or 2;

R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43} and R^{44} are, independently, C_{1-8} alkyl, C_{3-8} alkenyl, C_{3-8} alkynyl, C_{3-7} cycloalkyl, aryl, heteroaryl or heterocyclyl each or which is optionally substituted by halo, cyano, nitro, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, SCH_3, $S(O)CH_3$, $S(O)_2CH_3$, NH_2, $NHCH_3$, $N(CH_3)_2$, $NHC(O)NH_2$, $C(O)NH_2$, $NHC(O)CH_3$, $S(O)_2N(CH_3)_2$, $S(O)_2NHCH_3$, CF_3, CHF_2, CH_2F, CH_2CF_3 or OCF_3; and R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43} and R^{44} may additionally be hydrogen;

R^8, R^9, R^{10}, R^{13}, R^{14}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{23}, R^{24}, R^{45} and R^{47} are, independently, hydrogen, alkyl {optionally substituted by halo, hydroxy, C_{1-6} alkoxy, C_{1-6} haloalkoxy, heterocyclyl or phenyl (itself optionally substituted by halo, hydroxy, cyano, C_{1-4} alkyl or C_{1-4} alkoxy)}, phenyl (itself optionally substituted by halo, hydroxy, nitro, $S(O)_kC_{1-4}$ alkyl, $S(O)_2NH_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3) or heteroaryl (itself optionally substituted by halo, hydroxy, nitro, $S(O)_kC_{1-4}$ alkyl, $S(O)_2NH_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy,

$C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3);

R^{22} is alkyl {optionally substituted by halo, hydroxy, C_{1-6} alkoxy, C_{1-6} haloalkoxy, heterocyclyl or phenyl (itself optionally substituted by halo, hydroxy, cyano, C_{1-4} alkyl or C_{1-4} alkoxy)}, phenyl (itself optionally substituted by halo, hydroxy, cyano, C_{1-4} alkyl or C_{1-4} alkoxy) or heteroaryl (itself optionally substituted by halo, hydroxy, cyano, C_{1-4} alkyl or C_{1-4} alkoxy);

the pairs of substituents: R^8 and R^9, R^{13} and R^{14}, R^{17} and R^{18}, R^{20} and R^{21}, R^{23} and R^{24}, R^{26} and R^{27}, R^{28} and R^{29}, R^{30} and R^{31}, R^{32} with either R^{33} or R^{34}, R^{33} and R^{34}, R^{35} and R^{36}, R^{37} and R^{38}, R^{39} and R^{40} and R^{43} and R^{44} may, independently, join to form a ring and such a ring may also comprise an oxygen, sulphur or nitrogen atom;

where for any of the foregoing heterocyclic groups having a ring –N(H)- moiety, that –N(H)- moiety may be optionally substituted by C_{1-4} alkyl (itself optionally substituted by hydroxy), $C(O)(C_{1-4}$ alkyl), $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$ or $S(O)_2(C_{1-4}$ alkyl);

a ring nitrogen and/or sulphur atom is optionally oxidised to form an *N*-oxide and/or an *S*-oxide;

foregoing heteroaryl or heterocyclyl rings are *C*- or, where possible, *N*-linked;

or a pharmaceutically acceptable salt thereof or a solvate thereof.

Certain compounds of the present invention can exist in different isomeric forms (such as enantiomers, diastereomers, geometric isomers or tautomers). The present invention covers all such isomers and mixtures thereof in all proportions.

Suitable salts include acid addition salts such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate.

The compounds of the invention may exist as solvates (such as hydrates) and the present invention covers all such solvates.

Alkyl groups and moieties are straight or branched chain and are, for example, methyl, ethyl, n-propyl or iso-propyl.

Alkenyl and alkynyl groups and moieties are, for example, vinyl, allyl or propargyl.

Cycloalkyl is a mono-, bi- or tri-cyclic structure such as, for example, cyclopropyl, cyclopentyl, cyclohexyl or adamantyl.

Cycloalkenyl comprises one double bond and is, for example, cyclopentenyl or cyclohexenyl.

Acyl is, for example, carbonyl substituted by either C_{1-6} alkyl or optionally substituted phenyl.

Heterocyclyl is a non-aromatic 5 or 6 membered ring comprising at least one heteroatom selected from the group comprising nitrogen, oxygen and sulphur. Heterocyclyl is, for example, piperidinyl, morpholinyl, pyrrolidinyl, piperazinyl or tetrahydrofuryl.

Heteroaryl is an aromatic 5 or 6 membered ring comprising at least one heteroatom selected from the group comprising nitrogen, oxygen and sulphur. Heteroaryl is, for example, pyrrolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, thienyl, furyl, quinolinyl, isoquinolinyl, dihydroisoquinolinyl, indolyl, benzimidazolyl, benzo[b]furyl, benzo[b]thienyl, phthalazinyl, indanyl, oxadiazolyl or benzthiazolyl.

Aryl is a carbocyclic aromatic ring system (for example phenyl or naphthyl).

Arylalkyl is, for example, benzyl, 1-(phenyl)ethyl or 2-(phenyl)ethyl.

Heteroarylalkyl is, for example, pyridinylmethyl, pyrimidinylmethyl or 2-(pyridinyl)ethyl.

When R^{39} and R^{40} join to form a ring the ring is, for example, a piperazinyl, piperidinyl, pyrrolidinyl or morpholinyl ring.

In one aspect the invention provides a compound of formula (I) wherein X is C(O), $S(O)_2$ or a direct bond. In a further aspect X is C(O).

In another aspect the invention provides a compound of formula (I) wherein m and p are both 1.

In a further aspect the invention provides a compound of formula (I) wherein R^4, R^5, R^6 and R^7 are all hydrogen.

In yet another aspect the invention provides a compound of formula (I) wherein R^2 is hydrogen, C_{1-4} alkyl (optionally substituted by C_{3-6} cycloalkyl or phenyl), C_{3-4} alkenyl or C_{3-4} alkynyl. In another aspect R^2 is hydrogen.

In another aspect the invention provides a compound of formula (I) wherein R^2 is methyl, ethyl, allyl, cyclopropyl or propargyl.

In a further aspect the invention provides a compound of formula (I) wherein R^2 is methyl, ethyl or allyl.

In a still further aspect the invention provides a compound of formula (I) wherein R^2 is C_{3-8} alkenyl (such as allyl) or C_{3-7} cycloalkyl (such as cyclopropyl).

In a further aspect X is C(O).

In a still further aspect R^3 is $NR^{45}R^{46}$, aryl, heteroaryl, aryl(C_{1-4})alkyl or heteroaryl(C_{1-4})alkyl; R^{45} is hydrogen or C_{1-6} alkyl; R^{46} is aryl, heteroaryl, aryl(C_{1-4})alkyl or heteroaryl(C_{1-4})alkyl; wherein the aryl and heteroaryl groups of R^3 and R^{46} are independently substituted by $S(O)_qR^{25}$, $OC(O)NR^{26}R^{27}$, $NR^{32}C(O)NR^{33}R^{34}$ or $C(O)R^{41}$, and optionally further substituted by one or more of halo, cyano, nitro, hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy(C_{1-6})alkyl, $S(O)_qR^{25}$, $OC(O)NR^{26}R^{27}$, $NR^{28}R^{29}$, $NR^{30}C(O)R^{31}$, $NR^{32}C(O)NR^{33}R^{34}$, $S(O)_2NR^{35}R^{36}$, $NR^{37}S(O)_2R^{38}$, $C(O)NR^{39}R^{40}$, $C(O)R^{41}$, CO_2R^{42}, $NR^{43}CO_2R^{44}$, C_{3-10} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, phenyl, phenyl(C_{1-4})alkyl, phenoxy, phenylthio, phenyl(C_{1-4})alkoxy, heteroaryl, heteroaryl(C_{1-4})alkyl, heteroaryloxy or heteroaryl(C_{1-4})alkoxy; wherein any of the immediately foregoing phenyl and heteroaryl moieties are optionally substituted with halo, hydroxy, nitro, $S(O)_kC_{1-4}$ alkyl, $S(O)_2NH_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3; wherein q, k, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43} and R^{44} are as defined above.

In a still further aspect R^3 is $NR^{45}R^{46}$, phenyl, heteroaryl, phenyl(C_{1-4})alkyl or heteroaryl(C_{1-4})alkyl; R^{45} is hydrogen or C_{1-6} alkyl; R^{46} is phenyl, heteroaryl, phenyl(C_{1-4})alkyl or heteroaryl(C_{1-4})alkyl; wherein the phenyl and heteroaryl groups of R^3 and R^{46} are substituted by $S(O)_2R^{25}$, $OC(O)NR^{26}R^{27}$, $NR^{32}C(O)NR^{33}R^{34}$ or $C(O)R^{41}$, and optionally further substituted by one or more of halo, cyano, nitro, hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy(C_{1-6})alkyl, $S(O)_2R^{25}$, $OC(O)NR^{26}R^{27}$, $NR^{28}R^{29}$, $NR^{30}C(O)R^{31}$, $NR^{32}C(O)NR^{33}R^{34}$, $S(O)_2NR^{35}R^{36}$, $NR^{37}S(O)_2R^{38}$, $C(O)NR^{39}R^{40}$, $C(O)R^{41}$, CO_2R^{42}, $NR^{43}CO_2R^{44}$, C_{3-10} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy or C_{1-6} haloalkoxy; wherein R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43} and R^{44} are as defined above.

In another aspect R^3 is $NR^{45}R^{46}$, phenyl, heteroaryl, phenyl(C_{1-4})alkyl or heteroaryl(C_{1-4})alkyl; R^{45} is hydrogen or C_{1-6} alkyl; R^{46} is phenyl, heteroaryl, phenyl(C_{1-4})alkyl or heteroaryl(C_{1-4})alkyl; wherein the phenyl and heteroaryl groups of R^3 and R^{46} are substituted by $S(O)_2R^{25}$, and optionally further substituted by one or more of halo, cyano, nitro, hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy(C_{1-6})alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy or C_{1-6} haloalkoxy; wherein R^{25} is C_{1-6} alkyl.

In yet another aspect R^3 is $NR^{45}R^{46}$, phenyl or phenylCH_2; R^{45} is hydrogen or C_{1-2} alkyl; R^{46} is phenyl or phenylCH_2; wherein the phenyl groups of R^3 and R^{46} are mono-substituted by $S(O)_2R^{25}$; wherein R^{25} is C_{1-6} alkyl (for example methyl).

In a further aspect R^3 is phenyl or phenylCH_2; wherein the phenyl groups are mono-substituted (for example in the 4-position) by $S(O)_2R^{25}$; wherein R^{25} is C_{1-6} alkyl (for example methyl).

In another aspect R^3 is $NR^{45}R^{46}$, phenyl, heteroaryl, phenyl(C_{1-4})alkyl or heteroaryl(C_{1-4})alkyl; R^{45} is hydrogen or C_{1-6} alkyl; R^{46} is phenyl, heteroaryl, phenyl(C_{1-4})alkyl or heteroaryl(C_{1-4})alkyl; wherein the phenyl and heteroaryl groups of R^3 and R^{46} are substituted by $S(O)_2NR^{35}R^{36}$, and optionally further substituted by one or more of halo, cyano, nitro, hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy(C_{1-6})alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy or C_{1-6} haloalkoxy; wherein R^{35} and R^{36} are, independently, hydrogen, C_{1-8} alkyl, C_{3-8} alkenyl, C_{3-8} alkynyl, C_{3-7} cycloalkyl, aryl, heteroaryl or heterocyclyl each or which is optionally substituted by halo, cyano, nitro, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, SCH_3, $S(O)CH_3$, $S(O)_2CH_3$, NH_2, $NHCH_3$, $N(CH_3)_2$, $NHC(O)NH_2$, $C(O)NH_2$, $NHC(O)CH_3$, $S(O)_2N(CH_3)_2$, $S(O)_2NHCH_3$, CF_3, CHF_2, CH_2F, CH_2CF_3 or OCF_3.

In yet another aspect R^3 is $NR^{45}R^{46}$, phenyl or phenylCH_2; R^{45} is hydrogen or C_{1-2} alkyl; R^{46} is phenyl or phenylCH_2; wherein the phenyl groups of R^3 and R^{46} are mono-substituted by $S(O)_2NR^{35}R^{36}$; wherein R^{35} and R^{36} are, independently, hydrogen, C_{1-8} alkyl, C_{3-8} alkenyl, C_{3-8} alkynyl, C_{3-7} cycloalkyl, aryl, heteroaryl or heterocyclyl each or which is optionally substituted by halo, cyano, nitro, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, SCH_3, $S(O)CH_3$, $S(O)_2CH_3$, NH_2, $NHCH_3$, $N(CH_3)_2$, $NHC(O)NH_2$, $C(O)NH_2$, $NHC(O)CH_3$, $S(O)_2N(CH_3)_2$, $S(O)_2NHCH_3$, CF_3, CHF_2, CH_2F, CH_2CF_3 or OCF_3; where, in a further aspect, R^{35} is neither hydrogen nor C_{1-4} alkyl.

In another aspect the present invention provides a compound of formula (I) wherein X is C(O); and R^3 is C_{3-7} cycloalkyl, $(CH_2)_3$-aryl, $(CH_2)_3$-heteroaryl, (CH_2)aryl, (CH_2)-heteroaryl, $(CH_2)_3C(=O)NH$-aryl, $(CH_2)_3C(=O)NH$-heteroaryl, $(CH_2)C_{3-10}$ cycloalkyl, $(CH_2)_5NO_2$, $(CH_2)_5NC(=O)C_{1-4}$ alkyl, CH_2-CH=CH-aryl, CH_2-CH=CH-heteroaryl, NH-aryl, NH-heterocyclyl, NH-allyl, $NHCH_2$-aryl or $NHCH_2$-heteroaryl; wherein aryl, heteroaryl and heterocyclyl groups are optionally substituted as defined above.

In a further aspect the present invention provides a compound of formula (I) wherein X is C(O); and R^3 is $(CH_2)_3$-aryl, $(CH_2)_3$-heteroaryl, (CH_2)aryl, (CH_2)-heteroaryl,

$(CH_2)_3C(=O)NH$-aryl, $(CH_2)_3C(=O)NH$-heteroaryl, NH-aryl, NH-heterocyclyl, $NHCH_2$-aryl or $NHCH_2$-heteroaryl; wherein aryl, heteroaryl and heterocyclyl rings are optionally substituted as defined above.

In a still further aspect the present invention provides a compound of formula (I) wherein X is C(O); and R^3 is CH_2-phenyl (wherein the phenyl ring is optionally substituted at the 3-, 4- and/or 5- position with one or more substituents recited for aryl above), $(CH_2)_3$-phenyl, $(CH_2)_3$-oxadiazole-aryl, $(CH_2)_3$-oxadiazole-heteroaryl, $(CH_2)_3C(=O)NH$-phenyl, $NHCH_2$-phenyl, $NHCH_2$-heteroaryl or NH-phenyl (wherein the phenyl ring is optionally substituted at the 3-, 4- and/or 5- position with one or more substituents recited for aryl above); wherein aryl and heteroaryl rings are optionally substituted as defined above; phenyl rings are, unless stated otherwise, optionally substituted with one or more substituents recited for aryl above.

In yet another aspect the present invention provides a compound of formula (I) wherein X is C(O); and R^3 is CH_2-phenyl [wherein the phenyl ring is optionally substituted at the 3-, 4- and/or 5- position with one or more of Cl, Br, F, OH, C_{1-4} alkoxy (such as OMe or OEt), CN, $S(O)_2(C_{1-4}$ alkyl) (such as $S(O)_2Me$), $S(O)(C_{1-4}$ alkyl) (such as S(O)Me), $S(C_{1-4}$ alkyl) (such as SMe), $S(O)_2NH_2$, $S(O)_2N(C_{1-4}$ alkyl)$_2$ (such as $S(O)_2NMe_2$), C_{1-4} alkyl (such as Me), CF_3, OCF_3, NO_2, $NHC(O)(C_{1-4}$ alkyl) (such as NHCOMe), $C(O)(C_{1-4}$ alkyl) (such as C(O)Me), $S(O)_2CF_3$, $S(O)CF_3$, SCF_3, $C(O)NH_2$ or $CO_2(C_{1-4}$ alkyl) (such as CO_2Me)], $NHCH_2$-phenyl [wherein the phenyl ring is optionally substituted at the 3-, 4- and/or 5- position with one or more of Cl, Br, F, OH, C_{1-4} alkoxy (such as OMe or OEt), CN, $S(O)_2(C_{1-4}$ alkyl) (such as $S(O)_2Me$), $S(O)(C_{1-4}$ alkyl) (such as S(O)Me), $S(C_{1-4}$ alkyl) (such as SMe), $S(O)_2NH_2$, $S(O)_2N(C_{1-4}$ alkyl)$_2$ (such as $S(O)_2NMe_2$), CF_3, OCF_3, NO_2, $NHC(O)(C_{1-4}$ alkyl) (such as NHC(O)Me), $C(O)(C_{1-4}$ alkyl) (such as C(O)Me), $S(O)_2CF_3$, $S(O)CF_3$, SCF_3, $C(O)NH_2$ or $CO_2(C_{1-4}$ alkyl) (such as CO_2Me)] or NH-phenyl [wherein the phenyl ring is optionally substituted at the 3-, 4- and/or 5- position with one or more of F, Cl, C_{1-4} alkoxy (such as OMe) or $N(C_{1-4}$ alkyl)$_2$ (such as NMe_2)].

In another aspect the present invention provides a compound of formula (I) wherein X is C(O); and R^3 is CH_2-phenyl [wherein the phenyl ring is optionally substituted at the 4-position with Cl, Br, F, OH, OMe, CN, $S(O)_2Me$, $S(O)_2NH_2$, $S(O)_2NMe_2$, CF_3, OCF_3, NO_2, NHC(O)Me or CO_2Me], $NHCH_2$-phenyl [wherein the phenyl ring is optionally substituted at

the 4-position with Cl, Me, F or OMe] or NH-phenyl [wherein the phenyl ring is optionally substituted at the 4-position with F, Cl, OMe or NMe_2].

In a further aspect the invention provides a compound as hereinbefore defined wherein R^1 is C_{1-6} alkyl {optionally substituted by cyano, $NR^{13*}C(O)R^{14*}$, $NR^{15*}R^{16*}$, phenyl (itself optionally substituted by halo, hydroxy, nitro, $S(O)_kC_{1-4}$ alkyl, $S(O)_2NH_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3) or heteroaryl (itself optionally substituted by halo, hydroxy, nitro, $S(O)_kC_{1-4}$ alkyl, $S(O)_2NH_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3, OCF_3 or phenyl (itself optionally substituted by halo, hydroxy, nitro, $S(O)_kC_{1-4}$ alkyl, $S(O)_2NH_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3))} or C_{2-6} alkenyl {optionally substituted by phenyl (itself optionally substituted by halogen, hydroxy, nitro, C_{1-4} alkyl, C_{1-4} alkoxy or di(C_{1-4} alkyl)amino)}; R^{13*} is C_{1-4} alkyl; R^{14*} is phenyl optionally substituted by halo, hydroxy, nitro, $S(O)_kC_{1-4}$ alkyl, $S(O)_2NH_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3; and R^{15*} and R^{16*} are, independently, C_{1-4} alkyl or phenyl (optionally substituted by halo, hydroxy, nitro, $S(O)_kC_{1-4}$ alkyl, $S(O)_2NH_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3). Heteroaryl is, for example, pyrrolyl, furyl, indolyl or pyrimidinyl.

In another aspect R^1 is a three-carbon chain which optionally carries one methyl group along its length (for example a methyl group is carried on the carbon that bonds to the nitrogen atom of the ring shown in formula (I)) wherein said three-carbon chain is optionally substituted as described for R^1 above.

In a still further aspect the invention provides a compound as hereinbefore defined wherein R^1 is 2,6-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4-dimethoxy-6-hydroxybenzyl, 3-(4-dimethylamino-phenyl)prop-2-enyl, (1-phenyl-2,5-dimethylpyrrol-3-yl)methyl, 2-phenylethyl, 3-phenylpropyl, 3-R/S-phenylbutyl, 3-cyano-3,3-diphenylpropyl, 3-cyano-3-phenylpropyl, 4-(*N*-methylbenzamido)-3-phenylbutyl or 3,3-diphenylpropyl.

Further examples of R^1 include each individual partial structure presented in Schedule I and each individual partial structure presented in Schedule I can be combined with any definition of X, R^2, R^3 R^4, R^5, R^6, R^7, m or p as herein defined.

In another aspect the invention provides a compound as hereinbefore defined wherein R^1 is 3-R/S-phenylbutyl or, preferably, 3,3-diphenylpropyl. In a further aspect R^1 is 3-(S)-phenylbutyl. In yet a further aspect R^1 is 3,3-diphenylpropyl.

In a still further aspect the present invention provides a compound of formula (I) wherein R^1 is a hereinbefore defined; R^2 is ethyl, allyl or cyclopropyl (for example allyl or cyclopropyl); and R^3 is $NHCH_2C_6H_5$, $NHCH_2(4\text{-}F\text{-}C_6H_4)$, $NHCH_2(4\text{-}S(O)_2CH_3\text{-}C_6H_4)$, $NHCH_2(4\text{-}S(O)_2NH_2\text{-}C_6H_4)$, $CH_2C_6H_5$, $CH_2(4\text{-}F\text{-}C_6H_4)$, $CH_2(4\text{-}S(O)_2CH_3\text{-}C_6H_4)$ or $CH_2(4\text{-}S(O)_2NH_2\text{-}C_6H_4)$ {for example $NHCH_2(4\text{-}S(O)_2CH_3\text{-}C_6H_4)$ or $CH_2(4\text{-}S(O)_2CH_3\text{-}C_6H_4)$}.

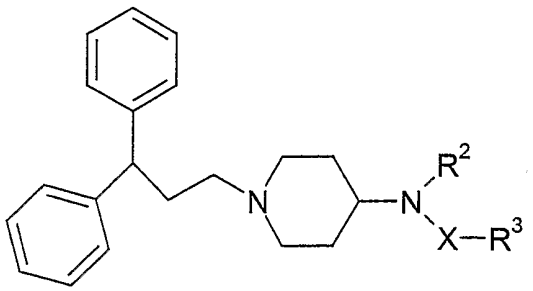
In yet another aspect the present invention provides a compound of formula (I) wherein R^1 is 3,3-diphenylpropyl, X is CO, R^2 is $C_{1\text{-}8}$ alkyl, and R^3 is as hereinbefore defined.

In a further aspect the present invention provides a compound of formula (I) wherein R^1 is 3,3-diphenylpropyl, X is CO, R^2 is allyl, and R^3 is as hereinbefore defined.

In a still further aspect the present invention provides a compound of formula (I) wherein R^1 is 3,3-diphenylpropyl or 3-R/S-phenylbutyl, X is C(O), R^2 is H, and R^3 is as hereinbefore defined.

In another aspect the present invention provides a compound of formula (I) wherein R^1 is 3,3-diphenylpropyl or 3-R/S-phenylbutyl, X is C(O), R^2 is H or methyl, and R^3 is $NR^{45}R^{46}$ (such as an amine group as hereinbefore defined for R^3).

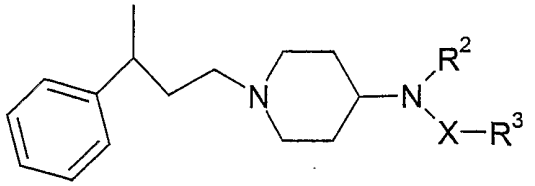
In yet another aspect the present invention provides a compound of formula (Ia):



(Ia)

wherein X, R^2 and R^3 are as defined above.

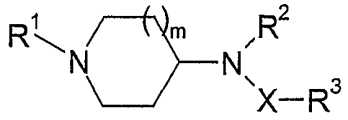
In a further aspect the present invention provides a compound of formula (Ib):



(Ib)

wherein X, R^2 and R^3 are as defined above.

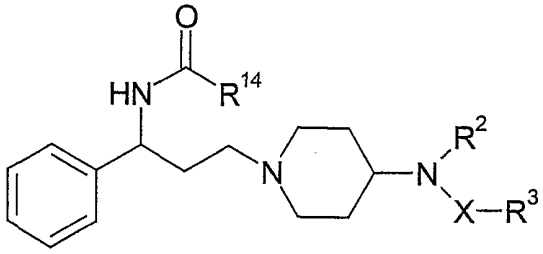
In a still further aspect the present invention provides a compound of formula (Ic):



(Ic)

wherein X, m, R^1, R^2 and R^3 are as defined above.

In yet another aspect the present invention provides a compound of formula (Id):



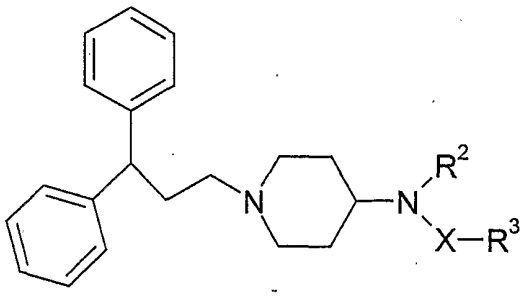
(Id)

wherein X, R^2 and R^3 are as defined above; and R^{14} is hydrogen, alkyl {optionally substituted by halo, hydroxy, C_{1-6} alkoxy, C_{1-6} haloalkoxy, heterocyclyl or phenyl (itself optionally substituted by halo, hydroxy, cyano, C_{1-4} alkyl or C_{1-4} alkoxy)}, phenyl (itself optionally substituted by halo, hydroxy, nitro, $S(O)_kC_{1-4}$ alkyl, $S(O)_2NH_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3), heteroaryl (itself optionally substituted by halo, hydroxy, nitro, $S(O)_kC_{1-4}$ alkyl, $S(O)_2NH_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3) or $NR^{20}R^{21}$; wherein R^{20} and R^{21}, together with the nitrogen to which they are attached, join to form an aziridine, azetidine or pyrrolidine ring.

The following compounds illustrate the invention.

TABLE I

Table I lists compounds of formula (Ia):



(Ia)

wherein X, R^2 and R^3 are listed in the table. Mass Spectrum details are given for certain compounds of Table I.

Compound No.	X	R^2	R^3	LCMS (MH+)
1	CO	Me	pyridin-4-yl	415
2	CO	Me	fur-3-yl	404
3	CO	Me	4-(4-OH-C_6H_4)C_6H_4	506
4	CO	Me	thien-3-yl	419
5	CO	Me	2-NO_2-thien-4-yl	464
6	CO	Me	pyrazin-2-yl	416
7	CO	Me	2,3-Cl_2-pyridin-5-yl	482
8	CO	Me	2-Cl-6-Me-pyridin-4-yl	462
9	CO	Me	3-Me-thien-2-yl	434
10	CO	Me	3-Me-fur-2-yl	418
11	CO	Me	2-CN-pyridin-5-yl	440
12	CO	Me	2-NO_2-thiazol-4-yl	477
13	CO	Me	$(CH_2)_5C_6H_5$	483
14	CO	Me	$(CH_2)_2$CONH(4-MeO-C_6H_4)	514
15	CO	Me	cyclopent-1-en-1-yl	403
16	CO	Me	$(CH_2)_7COC_6H_5$	540
17	CO	Me	4-tert-butyl-cyclohexyl	476
18	CO	Me	2-Me-4,5,6,7-F_4-benzofur-3-yl	539
19	CO	Me	$(CH_2)_3$(3,4-$(MeO)_2$-C_6H_3)	516
20	CO	Me	$(CH_2)_3$CONH(C_6H_5)	499
21	CO	Me	$(CH_2)_2$S(benzothiazol-2-yl)	530
22	CO	Me	$(CH_2)_3$CONH(2-CN-C_6H_4)	524
23	CO	Me	CH_2(1-phenyl-5-methyl-imidazol-4-yl)	508
24	CO	Me	CH_2(adamant-1-yl)	486
25	CO	Me	$(CH_2)_3$(1-Me-1,2-dihydro-isoquinolin-1-on-3-yl)	537
26	CO	Me	CH_2(4-hydroxy-phthalazin-1-yl)	496
27	CO	Me	CH_2(1-Me-cyclohexyl)	448

28	CO	Me	CH_2(indan-2-yl)	468
29	CO	Me	3-F-4-NO_2-C_6H_3	476
30	CO	Me	$CH_2NH(C_6H_5)$	443
31	CO	Me	$(CH_2)_5NO_2$	453
32	CO	Me	2-Cl-pyridin-4-yl	448
33	CO	Me	$(CH_2)_5NHCOCF_3$	517
34	CO	Me	CH_2(2-Me-3-NO_2-C_6H_3)	486
35	CO	Me	CH_2(3,5-$(MeO)_2$-C_6H_3)	488
36	CO	$CH_2CH=CH_2$	CH_2(4-EtO-C_6H_4)	497
37	CO	$CH_2CH=CH_2$	CH_2(5-F-indol-3-yl)	510
38	CO	$CH_2CH=CH_2$	CH_2(3,4-$(MeO)_2$-C_6H_3)	513
39	CO	$CH_2CH=CH_2$	CH_2(3,4,5-$(MeO)_3$-C_6H_2)	543
40	CO	$CH_2CH=CH_2$	$(CH_2)_3COC_6H_5$	509
41	CO	$CH_2CH=CH_2$	CH_2(indol-3-yl)	492
42	CO	$CH_2CH=CH_2$	CH_2(3,4-methylenedioxy-C_6H_3)	497
43	CO	$CH_2CH=CH_2$	CH_2(4-I-C_6H_4)	579
44	CO	$CH_2CH=CH_2$	CH_2(4-OCF_3-C_6H_4)	537
45	CO	$CH_2CH=CH_2$	CH_2(3-Me-4-MeO-C_6H_3)	497
46	CO	$CH_2CH=CH_2$	CH_2(3,4-$(MeO)_2$-C_6H_3)	527
47	CO	$CH_2CH=CH_2$	CH_2(3-CF_3-4-F-C_6H_3)	539
48	CO	$CH_2CH=CH_2$	CH_2(benzthien-3-yl)	509
49	CO	$CH_2CH=CH_2$	$(CH_2)_3$(3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl)	550
50	CO	$CH_2CH=CH_2$	$(CH_2)_3CO$(thien-2-yl)	515
51	CO	$CH_2CH=CH_2$	$(CH_2)_3$(4-Me-C_6H_4)	495
52	CO	$CH_2CH=CH_2$	CH_2(5-MeO-indol-3-yl)	522
53	$S(O)_2$	Me	2-OCF_3-C_6H_4	533
54	$S(O)_2$	Me	3-NO_2-4-Cl-C_6H_3	528
55	$S(O)_2$	Me	2,5-Cl_2-C_6H_3	517
56	$S(O)_2$	Me	2,5-Cl_2-thien-3-yl	523
57	$S(O)_2$	Me	2-Cl-5-CF_3-C_6H_3	551

58	$S(O)_2$	Me	2-Cl-thien-2-yl	489
59	$S(O)_2$	Me	2-Cl-4-CF_3-C_6H_3	551
60	$S(O)_2$	Me	2,4-F_2-C_6H_3	485
61	$S(O)_2$	Me	2,3-Cl_2-C_6H_3	517
62	$S(O)_2$	Me	2-NO_2-C_6H_4	494
63	$S(O)_2$	Me	3-Cl-4-(NHCOMe)-C_6H_3	540
64	$S(O)_2$	Me	2-CF_3-C_6H_4	517
65	$S(O)_2$	Me	3,5-Me_2-isoxazol-4-yl	468
66	$S(O)_2$	Me	2-(isoxazol-3-yl)thien-5-yl	522
67	$S(O)_2$	H	3-Cl-4-(NHCOMe)-C_6H_3	526
68	CO	Me	NH(3,4-Cl_2-C_6H_3)	496
69	CO	Me	NH(3-Cl-4-Me-C_6H_3)	476
70	CO	Me	NH(4-CF_3-C_6H_4)	496
71	CO	Me	NH(4-COMe-C_6H_4)	471
72	CO	Me	NH(2-Me-5-NO_2-C_6H_3)	487
73	CO	Me	NH(3,4-F_2-C_6H_3)	464
74	CO	Me	NH$(CH_2)_2$thien-2-yl	462
75	CO	Me	NH(4-I-C_6H_4)	554
76	CO	Me	NH(2-Et-C_6H_4)	457
77	CO	Me	NH(2,6-$(Me)_2$-C_6H_3)	457
78	CO	Me	$NHCH_2$(2,4-Cl_2-C_6H_3)	510
79	CO	H	$NHCH_2C_6H_5$	428
80	CO	H	NH(4-Br-C_6H_4)	494
81	CO	H	NH(4-Cl-C_6H_4)	448
82	CO	H	NH(2-Cl-C_6H_4)	448
83	CO	H	NH(4-Me-C_6H_4)	428
84	CO	H	NH(2,6-Me_2-4-Br-C_6H_2)	522
85	CO	H	NH(2,4,6-Me_3-C_6H_2)	456
86	CO	H	NH(2-NO_2-4-Me-C_6H_3)	473
87	CO	H	NH(3-NO_2-4-Me-C_6H_3)	473
88	CO	H	NH(2-Me-3-NO_2-C_6H_3)	473

89	CO	H	NH(4-MeO-C_6H_4)	444
90	CO	H	NH$(CH_2)_2$thien-2-yl	448
91	CO	H	NH-(n-propyl)	380
92	CO	H	NH(2,6-Me_2-C_6H_3)	442
93	CO	H	NH(2,6-F_2-C_6H_3)	450
94	CO	H	NH(4-NMe_2-C_6H_4)	457
95	CO	H	$NHCH_2$(2-Me-C_6H_4)	442
96	CO	Me	thien-2-yl	419
97	CO	Me	2-NO_2-thien-5-yl	448
98	CO	Me	3-NO_2-C_6H_4	458
99	CO	Me	4-NO_2-C_6H_4	458
100	CO	Me	4-F-C_6H_4	431
101	CO	Me	2-Cl-pyridin-5-yl	448
102	CO	Me	fur-2-yl	403
103	CO	Me	CH_2(4-Br-C_6H_4)	507
104	CO	Me	$(CH_2)_2CO_2Me$	423
105	CO	Me	cyclobutyl	391
106	CO	Me	$(CH_2)_3$(2-MeO-C_6H_4)	471
107	CO	Me	1-(4-MeO-C_6H_4)cyclopropyl	483
108	CO	Me	$(CH_2)_3$indol-3-yl	494
109	COCO	Me	$CH_2CH(CH_3)_2$	421
110	CO	Me	benzyl	427
111	CO	Me	CH_2(3,4-Cl_2-C_6H_3)	495
112	CO	Me	CH_2(tert-butyl)	407
113	CO	Me	CH_2(3,4,5-$(MeO)_3$-C_6H_2)	517
114	CO	Me	$CH_2CH(CH_3)_2$	393
115	CO	Me	$CH_2CH{=}CHC_6H_5$	453
116	CO	Me	$CH_2CH_2SCH_3$	411
117	CO	Me	CH_2(4-Cl-C_6H_4)	461
118	CO	Me	2,6-Cl_2-pyridin-3-yl	482
119	CO	Me	CH_2(2-F-C_6H_4)	445

120	CO	Me	$CH_2(3\text{-}F\text{-}C_6H_4)$	445
121	COCO	Me	phenyl	441
122	CO	Me	$CH_2(2\text{-}Cl\text{-}C_6H_4)$	461
123	CO	Me	$CH_2(3\text{-}Cl\text{-}C_6H_4)$	461
124	CO	Me	$CH_2(3\text{-}MeO\text{-}C_6H_4)$	457
125	CO	Me	$CH_2(3,4\text{-}(MeO)_2\text{-}C_6H_3)$	487
126	CO	Me	$CH_2(4\text{-}F\text{-}C_6H_4)$	445
127	CO	Me	$CH_2(4\text{-}MeO\text{-}C_6H_4)$	457
128	CO	Me	$CH_2(2,4\text{-}F_2\text{-}C_6H_3)$	463
129	CO	Me	CH_2(thien-2-yl)	433
130	CO	Me	CH_2(thien-3-yl)	433
131	CO	Me	CH_2(indol-3-yl)	466
132	CO	Me	$CH_2(2,4\text{-}Cl_2\text{-}C_6H_3)$	495
133	CO	Me	$CH_2(3,4\text{-}F_2\text{-}C_6H_3)$	463
134	CO	Me	$CH_2(4\text{-}CF_3\text{-}C_6H_4)$	495
135	CO	Me	$CH_2(4\text{-}CF_3O\text{-}C_6H_4)$	511
136	CO	Me	$CHMe(C_6H_5)$	441
137	CO	Me	CH_2(benzthien-3-yl)	483
138	CO	Me	$CH_2(4\text{-}NO_2\text{-}C_6H_4)$	472
139	CO	Me	$(CH_2)_3$(3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl)	524
140	CO	H	$CH_2(4\text{-}NO_2\text{-}C_6H_4)$	458
141	CO	H	$CH_2(3,4,5\text{-}(MeO)_3\text{-}C_6H_2)$	503
142	CO	H	$(CH_2)_3$(3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl)	510
143	CO	H	$CH_2(4\text{-}Cl\text{-}C_6H_4)$	447
144	CO	Me	$NH(3\text{-}Cl\text{-}C_6H_4)$	462
145	CO	Me	$NHCH_2C_6H_5$	442
146	CO	Me	NH(cyclohexyl)	434
147	CO	Me	NH(phenyl)	428
148	CO	Me	$NH(2\text{-}MeO\text{-}C_6H_4)$	458

149	CO	Me	NH(3-Me-C_6H_4)	442
150	CO	Me	NH(4-Br-C_6H_4)	508
151	CO	Me	NH(4-Cl-C_6H_4)	462
152	CO	Me	NH(4-NO_2-C_6H_4)	473
153	CO	Me	NH(2-Br-C_6H_4)	508
154	CO	Me	NH(4-CO_2Et-C_6H_4)	500
155	CO	Me	NH(2-F-C_6H_4)	446
156	CO	Me	NH(2-Cl-C_6H_4)	462
157	CO	Me	NH(4-Me-C_6H_4)	442
158	CO	Me	NH(2,4,6-Me_3-C_6H_2)	470
159	CO	Me	NH(2-NO_2-4-Me-C_6H_3)	487
160	CO	Me	NH(2-Me-4-Cl-C_6H_3)	476
161	CO	Me	NH(3-CN-C_6H_4)	453
162	CO	Me	NH(3-NO_2-4-Me-C_6H_3)	487
163	CO	Me	NH(3-COMe-C_6H_4)	470
164	CO	Me	NH(3,5-Me_2-C_6H_3)	456
165	CO	Me	NH(2,4-Me_2-C_6H_3)	456
166	CO	Me	NH(2-Cl-4-NO_2-C_6H_3)	507
167	CO	Me	NH(2-Me-3-NO_2-C_6H_3)	487
168	CO	Me	NH(4-MeO-C_6H_4)	458
169	CO	Me	NH(n-propyl)	394
170	CO	Me	NHEt	380
171	CO	Me	NH(2-phenyl-cyclopropyl)	468
172	CO	Me	NH($CH_2CH=CH_2$)	392
173	CO	Me	NH(naphth-2-yl)	478
174	CO	Me	NH$(CH_2)_2C_6H_5$	456
175	CO	Me	NH(2,6-Cl_2-pyridin-4-yl)	497
176	CO	Me	NH(2,6-F_2-C_6H_3)	464
177	CO	Me	NH(4-N(Me)$_2$-C_6H_4)	471
178	CO	Me	NH(naphth-1-yl)	478
179	CO	Me	NH(2-Me-C_6H_4)	442

180	CO	Me	NH(2,6-Cl_2-C_6H_3)	496
181	CO	Me	NH$(CH_2)_5CO_2$Et	494
182	bond	Me	CH_2(4-Cl-imidazol-3-yl)	424
183	bond	Me	CH_2(2-(4-NO_2-C_6H_4)fur-5-yl)	511
184	bond	Me	CH_2(3-OH-4-NO_2-C_6H_3)	461
185	bond	Me	CH_2(4-Br-imidazol-3-yl)	469
186	bond	Me	CH_2(1-(4-Cl-benzyl)-imidazol-3-yl)	514
187	bond	H	CH_2(3-NO_2-4-OH-C_6H_3)	447
188	bond	H	CH_2(3-OH-4-NO_2-C_6H_3)	447
189	CO	Me	CH_2(2,2-Me_2-3-(COMe)-cyclobutyl)	
190	CO	Me	CH_2(3-MeO-4-OH-C_6H_3)	
191	CO	Me	CH_2(5-OH-indol-3-yl)	
192	CO	Me	CH_2(5-F-indol-3-yl)	
193	CO	Me	CH_2(4-OH-C_6H_4)	443
194	CO	$CH_2C{\equiv}CH$	$(CH_2)_3$cyclohexyl	
195	CO	$CH_2C{\equiv}CH$	$CH_2CH_2CH(CH_3)C_6H_5$	
196	CO	$CH_2CH{=}CH_2$	$(CH_2)_3$cyclohexyl	
197	CO	$CH_2CH{=}CH_2$	CH_2(benzthien-3-yl)	
198	CO	$CH_2CH{=}CH_2$	CH_2(4-($S(O)_2$Me)-C_6H_4)	536
199	CO	CH_2cyclopropyl	$(CH_2)_3$cyclohexyl	
200	CO	$(CH_2)_2$phenyl	NH(2,4-F_2-C_6H_3)	
201	CO	H	NH(3,4-Cl_2-C_6H_3)	
202	CO	H	NH(2,4-Me_2-C_6H_3)	
203	CO	H	NH(2-Cl-4-NO_2-C_6H_3)	
204	CO	H	NH(4-MeO-C_6H_4)	
205	CO	H	$NHCH_2$(2,4-Cl_2-C_6H_3)	
206	CO	Me	CH_2(4-Me-C_6H_4)	441
207	CO	H	CH_2(3-Me-C_6H_4)	
208	CO	H	benzyl	

209	CO	H	$CH_2(4\text{-}EtO\text{-}C_6H_4)$	
210	CO	H	$CH_2(3\text{-}F\text{-}C_6H_4)$	
211	CO	H	$CH_2(4\text{-}iso\text{-}propyl\text{-}C_6H_4)$	
212	CO	H	CH_2-3-indole-5-OH	
213	CO	H	$CH_2(4\text{-}Me\text{-}C_6H_4)$	
214	CO	H	$CH_2(3\text{-}Me\text{-}4\text{-}MeO\text{-}C_6H_3)$	
215	CO	H	5-F-indol-3-yl	
216	CO	H	$CH_2(3,4\text{-}Cl_2\text{-}C_6H_3)$	
217	CO	H	$CH_2(4\text{-phenyl-}C_6H_4)$	
218	CO	H	$CH_2(3,4\text{-}F_2\text{-}C_6H_3)$	
219	CO	H	$CH_2(4\text{-}CF_3O\text{-}C_6H_4)$	497
220	CO	H	$CH_2(3\text{-Br-}4\text{-MeO-}C_6H_3)$	
221	CO	H	$CH_2(3\text{-}CF_3\text{-}4\text{-F-}C_6H_3)$	
222	CO	H	CH_2(benzthien-3-yl)	
223	CO	H	$CH_2(4\text{-}(S(O)_2NH_2)\text{-}C_6H_4)$	
224	CO	H	$CH_2(4\text{-}(S(O)_2NMe_2)\text{-}C_6H_4)$	
225	CO	H	$CH_2(3\text{-}CF_3\text{-}C_6H_4)$	
226	CO	H	$CH_2(3\text{-Br-}C_6H_4)$	
227	CO	H	$CH_2(4\text{-Br-}C_6H_4)$	
228	CO	H	$CH_2(4\text{-}(4\text{-F-}C_6H_4)\text{-}C_6H_4)$	
229	CO	Me	$NH(4\text{-}CF_3O\text{-}C_6H_4)$	
230	CO	Me	$NH(3\text{-F-}C_6H_4)$	
231	CO	Me	$NH(2,4\text{-}F_2\text{-}C_6H_3)$	
232	CO	H	$CH_2(4\text{-}NH_2\text{-}C_6H_4)$	
233	CO	$CH_2CH{=}CH_2$	$CH_2(3,5\text{-}(MeO)_2\text{-4-OH-}C_6H_2)$	529
234	CO	Me	$CH_2(4\text{-CN-}C_6H_4)$	452
235	CO	Me	$CH_2(4\text{-}(S(O)_2NH_2)\text{-}C_6H_4)$	506
236	CO	Me	$CH_2(4\text{-}(S(O)_2NMe_2)\text{-}C_6H_4)$	534
237	CO	H	$CH_2(3,4\text{-}(OMe)_2\text{-}C_6H_3)$	473
238	CO	H	$CH_2(4\text{-OMe-}C_6H_4)$	443
239	CO	H	$CH_2(4\text{-OH-}C_6H_4)$	429

240	CO	H	$CH_2(4\text{-}CF_3\text{-}C_6H_4)$	481
241	CO	H	$CH_2(4\text{-}F\text{-}C_6H_4)$	431
242	CO	H	$CH_2(3\text{-}CF_3\text{-}C_6H_4)$	
243	CO	$CH_2CH{=}CH_2$	$NH(4\text{-}F\text{-}C_6H_4)$	472
244	CO	$CH_2CH{=}CH_2$	$NH(4\text{-}CH_3\text{-}C_6H_4)$	468
245	CO	$CH_2CH{=}CH_2$	$NHCH_2C_6H_5$	468
246	CO	$CH_2CH{=}CH_2$	NH(phenyl)	454
247	CO	$CH_2CH{=}CH_2$	$NH(4\text{-}OCH_3\text{-}C_6H_4)$	484
248	CO	$CH_2CH{=}CH_2$	$NH((S)\text{-}CH_3CH(phenyl))$	482
249	CO	$CH_2CH{=}CH_2$	$NHCH_2CH{=}CH_2$	418
250	CO	$CH_2CH{=}CH_2$	$NHCH_2(3\text{-}CH_3\text{-}C_6H_4)$	482
251	CO	$CH_2CH{=}CH_2$	$NHCH_2(4\text{-}OCH_3\text{-}C_6H_4)$	498
252	CO	$CH_2CH{=}CH_2$	$NHCH_2(4\text{-}CH_3\text{-}C_6H_4)$	482
253	CO	$CH_2CH{=}CH_2$	$NHCH_2(4\text{-}F\text{-}C_6H_4)$	486
254	CO	Et	$CH_2(4\text{-}F\text{-}C_6H_4)$	459
255	CO	Et	$CH_2(4\text{-}Cl\text{-}C_6H_4)$	475
256	CO	Et	$CH_2(4\text{-}NO_2\text{-}C_6H_4)$	486
257	CO	Et	$CH_2(4\text{-}CN\text{-}C_6H_4)$	466
258	CO	Et	$CH_2(4\text{-}S(O)_2NH_2\text{-}C_6H_4)$	520
259	CO	Et	$CH_2(4\text{-}S(O)_2N(CH_3)_2\text{-}C_6H_4)$	548
260	CO	Et	$NH(4\text{-}Me\text{-}C_6H_4)$	456
261	CO	Et	$NH(CHCH_3C_6H_5)$	470
262	CO	Et	$NHCH_2CH{=}CH_2$	406
263	CO	Et	$NHCH_2C_6H_5$	456
264	CO	Et	$NHCH_2(3\text{-}Me\text{-}C_6H_4)$	470
265	CO	Et	$NHCH_2(4\text{-}OMe\text{-}C_6H_4)$	486
266	CO	Et	$NHCH_2(4\text{-}Me\text{-}C_6H_4)$	470
267	CO	Et	$NHCH_2(4\text{-}F\text{-}C_6H_4)$	474
268	CO	Me	$CH_2(4\text{-}(OCH_2C_6H_4)\text{-}C_6H_4)$	533
269	CO	$CH_2CH{=}CH_2$	$CH_2(3\text{-}F\text{-}C_6H_4)$	471
270	CO	$CH_2CH{=}CH_2$	$(CH_2)_3\text{-}3\text{-}(4\text{-}Cl\text{-}C_6H_4)\text{-}$	583

			[1,2,4]oxadiazol-5-yl	(585)
271	CO	$CH_2CH=CH_2$	$(CH_2)_3$-3-(3-NO_2-C_6H_4)-[1,2,4]oxadiazol-5-yl	594
272	CO	$CH_2CH=CH_2$	CH_2(3-OMe-C_6H_4)	483
273	CO	$CH_2CH=CH_2$	CH_2(4-Br-C_6H_4)	533/531
274	CO	$CH_2CH=CH_2$	CH_2(4-Cl-C_6H_4)	487 (489)
275	CO	$CH_2CH=CH_2$	CH_2(4-OMe-C_6H_4)	483
276	CO	$CH_2CH=CH_2$	CH_2(4-CF_3-C_6H_4)	521
277	CO	Me	CH_2(4-NHC(O)Me-C_6H_4)	484
278	CO	Me	CH_2(4-SMe-C_6H_4)	473
279	CO	Me	CH_2(4-CO_2Me-C_6H_4)	485
280	CO	$CH_2CH=CH_2$	CH_2(3,5-$(OMe)_2$-4-OH-C_6H_2)	529
281	CO	Me	CH_2(4-S(O)$_2$Me-C_6H_4)	505
282	CO	Et	CH_2(4-OCF_3-C_6H_4)	525
283	CO	Et	CH_2(4-S(O)$_2$Me-C_6H_4)	519
284	CO	cPr	CH_2(4-NO_2-C_6H_4)	498
285	CO	cPr	CH_2(4-OCF_3-C_6H_4)	537
286	CO	cPr	CH_2(4-S(O)$_2$Me-C_6H_4)	531
287	CO	cPr	CH_2(4-S(O)$_2$$NH_2$-$C_6H_4$)	532
288	CO	cPr	CH_2(4-F-C_6H_4)	471
289	CO	$(CH_2)_2OH$	CH_2(4-NO_2-C_6H_4)	502
290	CO	$(CH_2)_2OH$	CH_2(4-OCF_3-C_6H_4)	541
291	CO	$(CH_2)_2OH$	CH_2(4-S(O)$_2$Me-C_6H_4)	535
292	CO	$(CH_2)_2OH$	CH_2(4-S(O)$_2$$NH_2$-$C_6H_4$)	536
293	CO	$(CH_2)_2OH$	CH_2(4-F-C_6H_4)	475
294	CO	$(CH_2)_2F$	CH_2(4-NO_2-C_6H_4)	504
295	CO	$(CH_2)_2F$	CH_2(4-OCF_3-C_6H_4)	543
296	CO	$(CH_2)_2F$	CH_2(4-S(O)$_2$Me-C_6H_4)	537
297	CO	$(CH_2)_2F$	CH_2(4-S(O)$_2$$NH_2$-$C_6H_4$)	538

298	CO	$(CH_2)_2F$	$CH_2(4\text{-}F\text{-}C_6H_4)$	477
299	CO	$CH_2CH{=}CH_2$	$CH_2(4\text{-}NO_2\text{-}C_6H_4)$	498
300	CO	$CH_2CH{=}CH_2$	$CH_2(4\text{-}S(O)_2NH_2\text{-}C_6H_4)$	532
301	CO	$CH_2CH{=}CH_2$	$CH_2(4\text{-}F\text{-}C_6H_4)$	471
302	CO	cPr	CH_2(pyridin-2-yl)	454
303	CO	cPr	CH_2(1-Me-imidazol-4-yl)	457
304	CO	cPr	$CH_2(1\text{-}Me\text{-}4\text{-}NO_2\text{-}$pyrazol-5-yl)	502
305	CO	cPr	CH_2(6-Cl-pyridin-3-yl)	488 (490)
306	CO	cPr	$CH_2(3\text{-}Me\text{-}$isoxazol-5-yl)	458
307	CO	cPr	$CH_2(3,5\text{-}Me_2\text{-}$isoxazol-4-yl)	472
308	CO	Et	CH_2(5-Cl-thien-2-yl)	481 (483)
309	CO	Et	CH_2(5-($NHCO_2$-tert-Bu)-[2,4]oxadiazol-3-yl)	564
310	CO	Et	CH_2(6-Cl-pyridin-3-yl)	476 (478)
311	CO	Et	$CH_2(3,5\text{-}Me_2\text{-}$isoxazol-4-yl)	460
312	CO	Et	$CH_2(3\text{-}Me\text{-}$isoxazol-5-yl)	446
313	CO	Et	$CH_2(1\text{-}Me\text{-}4\text{-}NO_2\text{-}$pyrazol-5-yl)	490
314	CO	$(CH_2)_2$phenyl	$NH(2,4\text{-}F_2\text{-}C_6H_3)$	555
315	CO	H	$NH(2,4\text{-}Me_2\text{-}C_6H_3)$	422
316	CO	cPr	$NHCH_2C_6H_5$	468
317	CO	$(CH_2)_2OCONHCH_2$phenyl	$NHCH_2C_6H_5$	605
318	CO	$(CH_2)_2OH$	$NHCH_2C_6H_5$	472
319	CO	$(CH_2)_2F$	$NHCH_2C_6H_5$	474
320	CO	cPr	$NHCH_2(4\text{-}F\text{-}C_6H_4)$	486
321	CO	$(CH_2)_2OH$	$NHCH_2(4\text{-}F\text{-}C_6H_4)$	490
322	CO	$(CH_2)_2F$	$NHCH_2(4\text{-}F\text{-}C_6H_4)$	492
323	CO	Et	$NHCH_2(4\text{-}CF_3\text{-}C_6H_4)$	524

324	CO	Et	$NHCH_2$(thien-3-yl)	462
325	CO	Et	$NHCH_2$(indol-3-yl)	495
326	CO	Et	$NHCH_2$(5-OMe-indol-3-yl)	525
327	CO	Et	$NHCH_2$(2,5-F_2-C_6H_3)	492
328	CO	Et	$NHCH_2$(3-Cl-4-OH-C_6H_3)	507
329	CO	Et	$NHCH_2$(thien2-yl)	462
330	CO	Et	$NHCH_2$(3-OMe-C_6H_4)	486
331	CO	Et	$NHCH_2$(2,6-F_2-C_6H_3)	492
332	CO	Et	$NHCH_2$(3,5-F_2-C_6H_3)	492
333	CO	Et	$NHCH_2$(2-F-C_6H_4)	474
334	CO	Et	$NHCH_2$(4-OCF_3-C_6H_4)	540
335	CO	Et	$NHCH_2$(2,2-Me_2-3-C(O)Me-cBu)	504
336	CO	Et	$NHCH_2$(2-phenyl-5-Me-oxazol-4-yl)	537
337	CO	Et	NH(indazol-3-yl)	482
338	CO	Et	$NHCH_2$(4-$S(O)_2$Me-C_6H_4)	534
339	CO	Et	$NHCH_2$(2-OMe-C_6H_4)	486
340	CO	Et	$NHCH_2$(3,5-Me_2-isoxazol-4-yl)	475
341	CO	Et	$NHCH_2$(5-phenyl-[1,2,4]triazol-3-yl)	523
342	CO	Et	$NHCH_2$(5-CN-indol-3-yl)	520
343	CO	Et	$NHCH_2$(2,5-$(OMe)_2$-C_6H_3)	516
344	CO	Et	$NHCH_2$(3-F-C_6H_4)	474
345	CO	Et	$NHCH_2$(3,4-$(OMe)_2$-C_6H_3)	516
346	CO	Et	$NHCH_2$(3,4,5-$(OMe)_3$-C_6H_2)	546
347	CO	Et	$NHCH_2$(3-OH-C_6H_4)	472
348	CO	Et	$NHCH_2$(4-OH-C_6H_4)	472
349	CO	Et	$NHCH_2$-(3-F-4-OH-C_6H_3)	490
350	CO	Et	$NHCH_2$(3-OMe-4-OH-C_6H_3)	502
351	CO	Et	$NHCH_2$(4-NH_2-C_6H_4)	471
352	CO	Et	$NHCH_2$(3,5-$(OMe)_2$-4-OH-C_6H_2)	532
353	CO	Et	$NHCH_2$(3-NH_2-C_6H_4)	471
354	CO	Me	CH_2(4-($S(O)_2$NH-cPr)-C_6H_4)	546

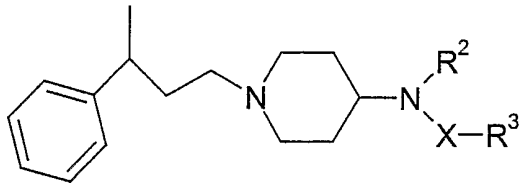
355	CO	Me	CH_2(4-($S(O)_2NH$-isoBu)-C_6H_4)	562
356	CO	Me	CH_2(4-($S(O)_2NH(CH_2)_2OMe$)-C_6H_4)	564
357	CO	Me	CH_2(4-($S(O)_2NH(CH_2)_2OH$)-C_6H_4)	550
358	CO	Me	CH_2(4-($S(O)_2NHCH_2C{\equiv}CH$)-C_6H_4)	544
359	CO	Me	CH_2(4-($S(O)_2NHCH_2CH{=}CH_2$)-C_6H_4)	546
360	CO	Me	CH_2(4-($S(O)_2NH(CH_2)_3OH$)-C_6H_4)	564
361	CO	Me	CH_2(4-($S(O)_2N(Me)CH_2C{\equiv}CH$)-$C_6H_4$)	558
362	CO	Me	CH_2(4-($S(O)_2N(Me)CH_2CH{=}CH_2$)-C_6H_4)	560
363	CO	Me	CH_2(4-($S(O)_2N(Me)Et$)-C_6H_4	548
364	CO	Me	CH_2-4-($S(O)_2N(Me)(CH_2)_2OH$)-C_6H_4)	564
365	CO	Me	CH_2(4-($S(O)_2NHCH_2$-cPr)-C_6H_4)	560
366	CO	Me	CH_2(4-($S(O)_2N(Me)$isoPr)-C_6H_4)	562
367	CO	Me	CH_2(4-($S(O)_2NHCH(Me)CH_2OH$)-C_6H_4)	564
368	CO	Me	CH_2(4-($S(O)_2$-azetidinyl)-C_6H_4)	546
369	CO	Me	CH_2(4-($S(O)_2$-pyrrolidinyl)-C_6H_4)	560
370	CO	Me	CH_2(4-($S(O)_2$-morpholin-4-yl)-C_6H_4)	576
371	CO	Me	CH_2(4-($S(O)_2NH$-isoPr)-C_6H_4)	548
372	CO	Me	CH_2(4-($S(O)_2NHMe$)-C_6H_4)	520
373	CO	Me	CH_2(4-($S(O)_2NHCH_2CH(Me)OH$)-C_6H_4)	564
374	CO	Me	CH_2(4-($S(O)_2$-3-CH_2OH-piperidin-1-yl)-C_6H_4)	604
375	CO	Me	CH_2(4-($S(O)_2NH(CH_2)_2$-imidazol-4-yl)-C_6H_4)	600
376	CO	Me	CH_2(4-($S(O)_2$-3-CH_2OH-pyrrolidin-1-yl)-C_6H_4)	590

377	CO	Me	CH_2(4-($S(O)_2$-3-OH-piperidin-1-yl)-C_6H_4)	590
379	CO	Me	CH_2(4-($S(O)_2$NH-pyridin-3-yl)-C_6H_4)	583
380	CO	Me	CH_2(4-($S(O)_2$NHCH_2CN)-C_6H_4)	545
381	CO	Me	CH_2(4-($S(O)_2$-pyrrolen-1-yl)-C_6H_4)	558
382	CO	Me	CH_2(4-($S(O)_2$-4-OH-piperidin-1-yl)-C_6H_4)	590
383	CO	Me	CH_2(4-($S(O)_2$NH-pyrazol-3yl)-C_6H_4)	572
384	CO	Me	CH_2(4-($S(O)_2$-3-OH-pyrrolidin-1-yl)-C_6H_4)	576
385	CO	Me	CH_2(4-($S(O)_2$NH$(CH_2)_2$OH)-C_6H_4)	514
386	CO	Me	CH_2(4-($S(O)_2$NH$(CH_2)_3$OH)-C_6H_4)	528
387	CO	Me	CH_2(4-($S(O)_2$NHCH_2CH(OH)Me)-C_6H_4)	528
388	CO	Me	NH(4-F-C_6H_4)	446
389	CO	Me	NHCH(Me)phenyl	456
390	CO	H	CH(CH_2CH=CH_2)-4-$S(O)_2$Me-C_6H_4	531
391	CO	Me	pyrrolidin-1yl	406
392	CO	H	CH_2(1,3-benzodioxol-5-yl)	395
393	CO	H	CH_2(4-NMe_2-C_6H_4)	394
394	CO	H	CH_2(3-Cl-4-OH-C_6H_3)	402 (404)
395	CO	H	CH_2(4-CO_2Me-C_6H_4)	409
396	CO	H	CH_2(3-CN-4-OH-C_6H_3)	392
397	CO	H	CH_2(3-F-4-(thiomorphlin-4-yl)-C_6H_3)	470
398	CO	H	CH_2(3-OMe-C_6H_4)	381
399	CO	H	CH_2(3-OH-C_6H_4)	367
400	CO	H	CH_2(3-F-4-OH-C_6H_3)	384
401	CO	Et	NHCH_2(4-$S(O)_2$Me-C_6H_4)	
402	CO	Et	NHCH_2(4-$S(O)_2NH_2$-C_6H_4)	
403	CO	Et	$CH_2C_6H_5$	

404	CO	$CH_2CH=CH_2$	$NHCH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	
405	CO	$CH_2CH=CH_2$	$NHCH_2(4\text{-}S(O)_2NH_2\text{-}C_6H_4)$	
406	CO	$CH_2CH=CH_2$	$CH_2C_6H_5$	
407	CO	cPr	$NHCH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	
408	CO	cPr	$NHCH_2(4\text{-}S(O)_2NH_2\text{-}C_6H_4)$	
409	CO	cPr	$CH_2C_6H_5$	

TABLE II

Table II comprises 409 compounds of formula (Ib):



(Ib)

wherein the variables X, R^2 and R^3 for each compound of Table II are the same as the correspondingly numbered compound in Table I. Mass Spectrum details are given for certain compounds of Table II.

Example Number	MS (MH+)
38	451
71	408
79	366
80	430
81	386
83	366
86	411
88	411
103	445
107	421
108	432
110	365
111	433
112	345
115	391
117	399
118	433
122	399
123	399
126	383
127	395
128	401
129	371
130	371
131	404
132	433
133	401
134	433

135	449
140	396
140 (R)	396
140 (S)	396
143 (R)	385 (387)
143 (S)	385 (387)
144	400
145	380
147	366
150	444
151	400
157	380
160	414
165	394
166	445
168	396
189	414
190	411
191	420
192	422
193	381
194	423
195	467
196	425
197	447
198	469
199	439
200	492
201	420
202	380
203	431

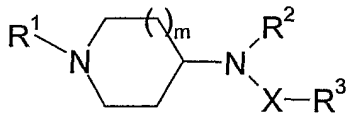
204	382
205	434
206	379
207	365
208	351
209	395
210	369
211	393
212	406
213	365
214	395
215	408
216	419
217	427
218	387
219	435
220	461
221	437
222	407
223	430
224	458
225	419
226	431
227	429 (431)
228	445
229	450
230	383
231	402
232	366
237	411
239	367

240	419
245	406
392	395
393	394
394	402 (404)
395	409

396	392
397	470
398	381
399	367
400	384

TABLE III

Table III discloses compounds of formula (Ic):



(Ic)

wherein the variables R^1, X, R^2 and R^3 are as defined in the Table below. Mass Spectrum details are given for certain compounds of Table III.

Compound No.	R^1	m	X	R^2	R^3	LCMS (MH+)
1	CH_2(2,6-$(MeO)_2$-C_6H_3)	1	CO	$(CH_2)_2$phenyl	NH(2,4-F_2-C_6H_3)	510
2	CH_2(2-(4-NO_2-C_6H_4)-fur-5-yl)	1	CO	$(CH_2)_2$phenyl	NH(2,4-F_2-C_6H_3)	561
3	CH_2(3-OH-4-NO_2-C_6H_3)	1	CO	$(CH_2)_2$phenyl	NH(2,4-F_2-C_6H_3)	511
4	CH_2(2-Et-fur-5-yl)	1	CO	$(CH_2)_2$phenyl	NH(2,4-F_2-C_6H_3)	468
5	CH_2(3-Me-C_6H_4)	1	CO	$(CH_2)_2$phenyl	NH(2,4-F_2-C_6H_3)	463
6	CH_2(2,4-MeO_2-pyrimidin-5-yl)	1	CO	$(CH_2)_2$phenyl	NH(2,4-F_2-C_6H_3)	512
7	CH_2(indol-3-yl)	1	CO	$(CH_2)_2$phenyl	NH(2,4-F_2-C_6H_3)	489
8	CH_2(1-phenyl-pyrrol-3-yl)	1	CO	$(CH_2)_2$phenyl	NH(2,4-F_2-C_6H_3)	515
9	$(CH_2)_3$phenyl	1	CO	$(CH_2)_2$phenyl	NH(2,4-F_2-C_6H_3)	464
10 ‡	iso-propyl	1	CO	4-Cl-C_6H_4	benzyl	
11	$(CH_2)_2C(C_6H_5)$(4-F-C_6H_4)OH	1	CO	Et	CH_2(4-$S(O)_2$Me-C_6H_4)	553
12	$(CH_2)_2CH(CH{=}CH_2)C_6H_5$	1	CO	Me	CH_2(4-F-C_6H_4)	395
13	$(CH_2)_2CH(C_6H_5)$azetidin-1-yl	1	CO	Me	CH_2(4-F-C_6H_4)	424

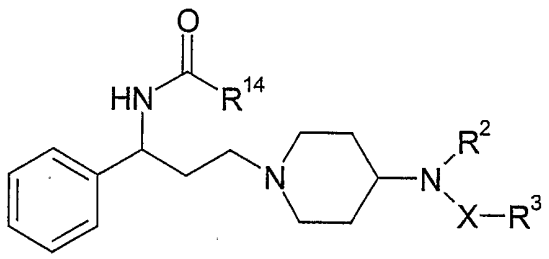
14	$(CH_2)_2CH(C_6H_5)$pyrrolidin-1-yl	1	CO	Me	$CH_2(4\text{-}F\text{-}C_6H_4)$	438
15	$(CH_2)_2CH(C_6H_5)(4\text{-}F\text{-}C_6H_4)$	1	CO	Me	$CH_2(4\text{-}F\text{-}C_6H_4)$	463
16	$(CH_2)_2CH(4\text{-}F\text{-}C_6H_4)_2$	1	CO	Me	$CH_2(4\text{-}F\text{-}C_6H_4)$	481
17	$(CH_2)_2CH(4\text{-}F\text{-}C_6H_4)_2$	1	CO	Me	$CH_2(4\text{-}S(O)_2NH_2\text{-}C_6H_4)$	542
18	$(CH2)_2N(C_6H_5)_2$	1	CO	$CH_2CH{=}CH_2$	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	532
19	$(CH2)_2N(C_6H_5)_2$	1	CO	Me	$CH_2(4\text{-}F\text{-}C_6H_4)$	446
20	$(CH_2)_2N(C_6H_5)CO(CH_2)_2(4\text{-}OH\text{-}C_6H_4)$	1	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	591
21	$(CH_2)_2N(C_6H_5)CO(2\text{-}SMe$-pyridin-3-yl)	1	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	595
22	$(CH_2)_2N(C_6H_5)CO(2\text{-}OH\text{-}5\text{-}F\text{-}C_6H_3)$	1	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	580 (M-H)
23	$(CH_2)_2CH(C_6H_5)NH_2$	1	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	458
24	$(CH_2)_2NHC_6H_5$	1	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	444
25	$(CH_2)_2NHC_6H_5$	1	CO	Et	$CH_2(4\text{-}F\text{-}C_6H_4)$	384
26	$(CH_2)_2CH(OH)C_6H_5$	1	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	459
27	$CH(Me)CH_2CH(C_6H_5)_2$	1	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	533
28	$CH(Me)(CH_2)_2C_6H_5$	1	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	457
29	$(CH_2)_2CH(Me)(3\text{-}CF_3\text{-}C_6H_4)$	1	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	525
30	$(CH_2)_2CH(Me)(3\text{-}Cl\text{-}C_6H_4)$	1	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	491

31	$(CH_2)_2CH(Me)C_6H_5$	1	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	457
32	$(CH_2)_2CH(Me)(3,4\text{-}Cl_2\text{-}C_6H_3)$	1	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	525
33	$(CH_2)_2CH(C_6H_5)_2$	0	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	477
34	$(CH_2)_2CH(4\text{-}Cl\text{-}C_6H_4)$4-pyridyl	1	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	554
35	$(CH_2)_2CH(4\text{-}Cl\text{-}C_6H_4)$2-pyridyl	1	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	554
36	$(CH_2)_2CH(C_6H_5)$-(1,3-benzodioxol-5-yl)	1	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	563
37	$(CH_2)_2CH(C_6H_5)(4\text{-}Cl\text{-}C_6H_4)$	1	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	553
38	$(CH_2)_2CH(C_6H_5)(3,4\text{-}Cl_2\text{-}C_6H_3)$	1	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	587
39	$(CH_2)_2CH(C_6H_5)(4\text{-}MeO\text{-}C_6H_4)$	1	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	549
40	$(CH_2)_2CH(C_6H_5)(3\text{-}Cl\text{-}C_6H_4)$	1	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	553
41	$(CH_2)_2CH(C_6H_5)(4\text{-}Me\text{-}C_6H_4)$	1	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	533
42	$(CH_2)_2CH(C_6H_5)(4\text{-}CF_3\text{-}C_6H_4)$	1	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	587
43	$(CH_2)_2CH(4\text{-}F\text{-}C_6H_4)_2$	1	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	555
44	$(CH_2)_2CH(4\text{-}F\text{-}C_6H_4)_2$	1	CO	$CH_2CH{=}CH_2$	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	567

‡ Ref: Stefan Sanczuk, Hubert K. F. Hermans (Janssen Pharmaceutica N. V., Belg.). Chemical Abstracts 87: 53094.

TABLE IV

Table IV discloses compounds of formula (Id):



(Id)

wherein the variables R^{14}, X, R^2 and R^3 are as defined in the Table below. Mass Spectrum details are given for certain compounds in Table IV.

Compound No.	X	R^2	R^3	R^{14}	LCMS (MH+)
1	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	phenyl	562
2	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	iso-Pr	528
3	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	$CH(CH_2CH_3)_2$	556
4	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	$CH(CH_3)CH_2CH_2CH_3$	556
5	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	$CH_2C(CH_3)_3$	556
6	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	$CH_2CH(CH_3)_2$	542
7	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	$CH_2CH(CH_3)CH_2CH_3$	556
8	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	Et	514
9	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	$CH_2CH_2CH(CH_3)_2$	556
10	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	n-Pr	528
11	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	1-Me-pyrrol-2-yl	565
12	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	furan-2-yl	552
13	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	tert-Bu	542
14	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	$C(CH_3)_2CH_2CH_3$	556
15	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	CH_2OEt	544
16	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	n-Bu	542
17	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	n-pentyl	556
18	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	$C(OH)Me_2$	544
19	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	pyrrol-2-yl	551
20	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	furan-3-yl	552

21	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	thien-2-yl	568
22	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	thien-3-yl	568
23	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	pyrazin-2-yl	564
24	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	pyridin-2-yl	563
25	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	pyridin-3-yl	563
26	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	pyridin-4-yl	563
27	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	3-Me-furan-2-yl	566
28	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	CH_2CH_2OMe	544
29	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	CH_2CH_2OEt	558
30	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	$CH(OH)CH_2CH_2CH_3$	558
31	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	2-Me-furan-3-yl	566
32	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	4-Me-oxazol-5-yl	567
33	CO	Et	$NHCH_2C_6H_5$	azetidin-1-yl	
34	CO	Et	$NHCH_2(4\text{-}F\text{-}C_6H_4)$	azetidin-1-yl	
35	CO	Et	$NHCH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	azetidin-1-yl	
36	CO	Et	$NHCH_2(4\text{-}S(O)_2NH_2\text{-}C_6H_4)$	azetidin-1-yl	
37	CO	Et	$CH_2C_6H_5$	azetidin-1-yl	
38	CO	Et	$CH_2(4\text{-}F\text{-}C_6H_4)$	azetidin-1-yl	
39	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	azetidin-1-yl	
40	CO	Et	$CH_2(4\text{-}S(O)_2NH_2\text{-}C_6H_4)$	azetidin-1-yl	
41	CO	allyl	$NHCH_2C_6H_5$	azetidin-1-yl	
42	CO	allyl	$NHCH_2(4\text{-}F\text{-}C_6H_4)$	azetidin-1-yl	
43	CO	allyl	$NHCH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	azetidin-1-yl	
44	CO	allyl	$NHCH_2(4\text{-}S(O)_2NH_2\text{-}C_6H_4)$	azetidin-1-yl	
45	CO	allyl	$CH_2C_6H_5$	azetidin-1-yl	
46	CO	allyl	$CH_2(4\text{-}F\text{-}C_6H_4)$	azetidin-1-yl	
47	CO	allyl	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	azetidin-1-yl	

48	CO	allyl	$CH_2(4\text{-}S(O)_2NH_2\text{-}C_6H_4)$	azetidin-1-yl	
49	CO	cPr	$NHCH_2C_6H_5$	azetidin-1-yl	
50	CO	cPr	$NHCH_2(4\text{-}F\text{-}C_6H_4)$	azetidin-1-yl	
51	CO	cPr	$NHCH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	azetidin-1-yl	
52	CO	cPr	$NHCH_2(4\text{-}S(O)_2NH_2\text{-}C_6H_4)$	azetidin-1-yl	
53	CO	cPr	$CH_2C_6H_5$	azetidin-1-yl	
54	CO	cPr	$CH_2(4\text{-}F\text{-}C_6H_4)$	azetidin-1-yl	
55	CO	cPr	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	azetidin-1-yl	
56	CO	cPr	$CH_2(4\text{-}S(O)_2NH_2\text{-}C_6H_4)$	azetidin-1-yl	
57	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	$2\text{-}F\text{-}C_6H_4$	580
58	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	$2,6\text{-}F_2\text{-}C_6H_3$	598
59	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	$2\text{-}Cl\text{-}C_6H_4$	596
60	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	$2\text{-}MeO\text{-}C_6H_4$	592
61	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	$3\text{-}CN\text{-}C_6H_4$	587
62	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	$3\text{-}F\text{-}C_6H_4$	580
63	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	$3\text{-}MeO\text{-}C_6H_4$	592
64	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	$3\text{-}Me\text{-}C_6H_4$	576
65	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	$4\text{-}CN\text{-}C_6H_4$	587
66	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	$4\text{-}F\text{-}C_6H_4$	580
67	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	$4\text{-}Cl\text{-}C_6H_4$	596
68	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	$4\text{-}(COCH_3)C_6H_4$	604
69	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	$4\text{-}Me\text{-}C_6H_4$	576
70	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	$CH(Me)C_6H_5$	590
71	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	$CH_2(2\text{-}F\text{-}C_6H_4)$	594
72	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	$CH_2(2\text{-}MeO\text{-}C_6H_4)$	606
73	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	$CH_2(3\text{-}MeO\text{-}C_6H_4)$	606
74	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	$CH_2(4\text{-}F\text{-}C_6H_4)$	594
75	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	$CH_2(4\text{-}MeO\text{-}C_6H_4)$	606
76	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	indol-5-yl	601

77	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	6-Cl-pyridin-3-yl	597
78	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	$2\text{-}NO_2\text{-}C_6H_4$	607
79	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	$3\text{-}NO_2\text{-}C_6H_4$	607
80	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	$4\text{-}NO_2\text{-}C_6H_4$	607
81	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	$3,4\text{-}F_2\text{-}C_6H_3$	598
82	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	benztriazol-4-yl	603
83	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	2-Me-pyridin-3-yl	577
84	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	6-Me-pyridin-2-yl	577
85	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	$CH(OMe)C_6H_5$	606
86	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	5-Me-pyrazin-2-yl	578
87	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	dihydrobenzofuran-4-yl	604
88	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	2-OMe-pyridin-3-yl	593
89	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	6-Cl-pyridin-2-yl	597
90	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	2-Cl-pyridin-4-yl	597
91	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	1*H*-pyridin-2-on-6-yl	579
92	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	indol-7-yl	601
93	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	dihydrobenzofuran-7-yl	604
94	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	6-CN-pyridin-3-yl	588
95	CO	Et	$CH_2(4\text{-}S(O)_2Me\text{-}C_6H_4)$	2-F-pyridin-3-yl	581

The following abbreviations are used in Tables I to IV:

Me = methyl	Et = ethyl
Pr = propyl	Bu = butyl
cPr = cyclopropyl	cBu = cyclobutyl

The compounds of formula (I), (Ia), (Ib), (Ic) or (Id) can be prepared as shown in the processes on pages marked Schemes 1 to 14 below. (In Scheme 10 suitable coupling agents include HATU (O-(7-Azabenzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium hexafluorophosphate) and PyBROP (bromo-*tris*-pyrrolidinophosphonium hexafluoro-phosphate) which may be employed according to Example 26.) The starting materials for these processes are either commercially available or can be prepared either by literature

methods or by adapting literature methods. In the Schemes the variables R^{1*}, R^{2*} and R^{3*} have been used where the group R^1, R^2 or R^3 is, respectively, CH_2R^{1*}, CH_2R^{2*} or CH_2R^{3*}; Ac is $CH_3C(O)$; and Ar^1 and Ar^2 denote aromatic rings which are optionally substituted. Although Schemes 1-14 are depicted for m and p = 1, and R^4, R^5, R^6 and R^7 as hydrogen, it is clear that they can be readily adapted for alternative values of m, p, R^4, R^5, R^6 and R^7.

In a further aspect the invention provides processes for preparing the compounds of formula (I), (Ia), (Ib), (Ic) and (Id). Many of the intermediates in the processes are novel and these are provided as further features of the invention.

The compounds of the invention have activity as pharmaceuticals, in particular as modulators (such as agonists, partial agonists, inverse agonists or antagonists) of chemokine receptor (especially CCR5) activity, and may be used in the treatment of autoimmune, inflammatory, proliferative or hyperproliferative diseases, or immunologically-mediated diseases (including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS)). Examples of these conditions are:

(1) (the respiratory tract) obstructive diseases of airways including: chronic obstructive pulmonary disease (COPD) (such as irreversible COPD); pulmonary fibrosis; asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; bronchitis {such as eosinophilic bronchitis}; acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis; sarcoidosis; farmer's lung and related diseases; nasal polyposis; fibroid lung or idiopathic interstitial pneumonia;

(2) (bone and joints) arthrides including rheumatic, infectious, autoimmune, seronegative spondyloarthropathies (such as ankylosing spondylitis, psoriatic arthritis or Reiter's disease), Behçet's disease, Sjogren's syndrome or systemic sclerosis;

(3) (skin and eyes) psoriasis, atopic dermatitis, contact dermatitis or other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Phemphigus, bullous Phemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides erythemas, cutaneous eosinophilias, uveitis, Alopecia areata or vernal conjunctivitis;

(4) (gastrointestinal tract) Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, irritable bowel disease or food-related allergies which have effects remote from the gut (for example migraine, rhinitis or eczema);

(5) (Allograft rejection) acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea; or chronic graft versus host disease; and/or

(6) (other tissues or diseases) Alzheimer's disease, multiple sclerosis, atherosclerosis, inhibiting the entry of viruses into target cells, Acquired Immunodeficiency Syndrome (AIDS), Lupus disorders (such as lupus erythematosus or systemic lupus), erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, leprosy (such as lepromatous leprosy), Peridontal disease, Sezary syndrome, idiopathic thrombocytopenia pupura, disorders of the menstrual cycle, glomerulonephritis or cerebral malaria.

The compounds of the present invention are also of value in inhibiting the entry of viruses (such as human immunodeficiency virus (HIV)) into target calls and, therefore, are of value in the prevention of infection by viruses (such as HIV), the treatment of infection by viruses (such as HIV) and the prevention and/or treatment of acquired immune deficiency syndrome (AIDS).

According to a further feature of the invention there is provided a compound of the formula (I), (Ia), (Ib), (Ic) or (Id), or a pharmaceutically acceptable salt thereof or a solvate thereof, for use in a method of treatment of a warm blooded animal (such as man) by therapy (including prophylaxis).

According to a further feature of the present invention there is provided a method for modulating chemokine receptor activity (especially CCR5 receptor activity) in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof or a solvate thereof.

The present invention also provides the use of a compound of the formula (I), (Ia), (Ib), (Ic) or (Id), or a pharmaceutically acceptable salt thereof or a solvate thereof, as a medicament, especially a medicament for the treatment of transplant rejection, respiratory disease, psoriasis or rheumatoid arthritis (especially rheumatoid arthritis). [Respiratory

disease is, for example, COPD, asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)} or rhinitis {acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis}; and is particularly asthma or rhinitis].

In another aspect the present invention provides the use of a compound of the formula (I), (Ia), (Ib), (Ic) or (Id), or a pharmaceutically acceptable salt thereof or a solvate thereof, in the manufacture of a medicament for use in therapy (for example modulating chemokine receptor activity (especially CCR5 receptor activity (especially rheumatoid arthritis)) in a warm blooded animal, such as man).

The invention also provides a compound of the formula (I), (Ia), (Ib), (Ic) or (Id), or a pharmaceutically acceptable salt thereof or a solvate thereof, for use as a medicament, especially a medicament for the treatment of rheumatoid arthritis.

In another aspect the present invention provides the use of a compound of the formula (I), (Ia), (Ib) or (Ic), or a pharmaceutically acceptable salt thereof or a solvate thereof, in the manufacture of a medicament for use in therapy (for example modulating chemokine receptor activity (especially CCR5 receptor activity (especially rheumatoid arthritis)) in a warm blooded animal, such as man).

The invention further provides the use of a compound of formula (I), (Ia), (Ib), (Ic) or (Id), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of:

(1) (the respiratory tract) obstructive diseases of airways including: chronic obstructive pulmonary disease (COPD) (such as irreversible COPD); asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; bronchitis {such as eosinophilic bronchitis}; acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor

rhinitis; sarcoidosis; farmer's lung and related diseases; nasal polyposis; fibroid lung or idiopathic interstitial pneumonia;

(2) (bone and joints) arthrides including rheumatic, infectious, autoimmune, seronegative spondyloarthropathies (such as ankylosing spondylitis, psoriatic arthritis or Reiter's disease), Behçet's disease, Sjogren's syndrome or systemic sclerosis;

(3) (skin and eyes) psoriasis, atopic dermatitis, contact dermatitis or other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Phemphigus, bullous Phemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides erythemas, cutaneous eosinophilias, uveitis, Alopecia areata or vernal conjunctivitis;

(4) (gastrointestinal tract) Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, irritable bowel disease or food-related allergies which have effects remote from the gut (for example migraine, rhinitis or eczema);

(5) (Allograft rejection) acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea; or chronic graft versus host disease; and/or

(6) (other tissues or diseases) Alzheimer's disease, multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), Lupus disorders (such as lupus erythematosus or systemic lupus), erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, leprosy (such as lepromatous leprosy), Peridontal disease, Sezary syndrome, idiopathic thrombocytopenia pupura or disorders of the menstrual cycle;

in a warm blooded animal, such as man.

The present invention further provides a method of treating a chemokine mediated disease state (especially a CCR5 mediated disease state) in a warm blooded animal, such as man, which comprises administering to a mammal in need of such treatment an effective amount of a compound of formula (I), (Ia), (Ib), (Ic) or (Id), or a pharmaceutically acceptable salt thereof or solvate thereof.

In order to use a compound of the invention, or a pharmaceutically acceptable salt thereof or solvate thereof, for the therapeutic treatment of a warm blooded animal, such as man, in particular modulating chemokine receptor (for example CCR5 receptor) activity, said

ingredient is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the formula (I), (Ia), (Ib), (Ic) or (Id), or a pharmaceutically acceptable salt thereof or a solvate thereof (active ingredient), and a pharmaceutically acceptable adjuvant, diluent or carrier. In a further aspect the present invention provides a process for the preparation of said composition which comprises mixing active ingredient with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by topical (such as to the lung and/or airways or to the skin), oral, rectal or parenteral administration. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, aerosols, dry powder formulations, tablets, capsules, syrups, powders, granules, aqueous or oily solutions or suspensions, (lipid) emulsions, dispersible powders, suppositories, ointments, creams, drops and sterile injectable aqueous or oily solutions or suspensions.

A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule which contains between 0.1mg and 1g of active ingredient.

In another aspect a pharmaceutical composition of the invention is one suitable for intravenous, subcutaneous or intramuscular injection.

Each patient may receive, for example, an intravenous, subcutaneous or intramuscular dose of 0.01mgkg^{-1} to 100mgkg^{-1} of the compound, preferably in the range of 0.1mgkg^{-1} to 20mgkg^{-1} of this invention, the composition being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively the intravenous dose may be given by continuous infusion over a period of time. Alternatively each patient will receive a daily oral dose which is

approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day.

The following illustrate representative pharmaceutical dosage forms containing the compound of formula (I), (Ia), (Ib), (Ic) or (Id), or a pharmaceutically acceptable salt thereof or a solvent thereof (hereafter Compound X), for therapeutic or prophylactic use in humans:

(a)

Tablet I	mg/tablet
Compound X	100
Lactose Ph.Eur.	179
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

(b)

Tablet II	mg/tablet
Compound X	50
Lactose Ph.Eur.	229
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

(c)

Tablet III	mg/tablet
Compound X	1.0
Lactose Ph.Eur.	92
Croscarmellose sodium	4.0
Polyvinylpyrrolidone	2.0
Magnesium stearate	1.0

(d)

Capsule	mg/capsule
Compound X	10
Lactose Ph.Eur.	389
Croscarmellose sodium	100
Magnesium stearate	1.0

(e)

Injection I	(50 mg/ml)
Compound X	5.0% w/v
Isotonic aqueous solution	to 100%

Buffers, pharmaceutically-acceptable cosolvents such as polyethylene glycol, polypropylene glycol, glycerol or ethanol or complexing agents such as hydroxy-propyl β-cyclodextrin may be used to aid formulation.

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C;

(ii) organic solutions were dried over anhydrous magnesium sulphate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30 mm Hg) with a bath temperature of up to 60°C;

(iii) chromatography unless otherwise stated means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates; where a "Bond Elut" column is referred to, this means a column containing 10g or 20g of silica of 40 micron particle size, the silica being contained in a 60ml disposable syringe and supported by a porous disc, obtained from Varian, Harbor City, California, USA under the name "Mega Bond Elut SI". Where an "Isolute™ SCX column" is referred to, this means a column containing benzenesulphonic acid (non-endcapped) obtained from International Sorbent Technology Ltd., 1st House, Duffryn Industial Estate, Ystrad Mynach, Hengoed, Mid Clamorgan, UK. Where "Argonaut™ PS-*tris*-amine scavenger resin" is referred to, this means a *tris*-(2-aminoethyl)amine polystyrene resin obtained from Argonaut Technologies Inc., 887 Industrial Road, Suite G, San Carlos, California, USA.

(iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(v) yields, when given, are for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vi) when given, ^{1}H NMR data is quoted and is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz using perdeuterio DMSO (CD_3SOCD_3) as the solvent unless otherwise stated; coupling constants (J) are given in Hz;

(vii) chemical symbols have their usual meanings; SI units and symbols are used;

(viii) solvent ratios are given in percentage by volume;

(ix) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (APCI) mode using a direct exposure probe; where indicated ionisation was effected by electrospray (ES); where values for m/z are given, generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(M+H)^+$;

(x) LCMS characterisation was performed using a pair of Gilson 306 pumps with Gilson 233 XL sampler and Waters ZMD4000 mass spectrometer. The LC comprised water symmetry 4.6x50 column C18 with 5 micron particle size. The eluents were: A, water with 0.05% formic acid and B, acetonitrile with 0.05% formic acid. The eluent gradient went from 95% A to 95% B in 6 minutes. Where indicated ionisation was effected by electrospray (ES); where values for m/z are given, generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(M+H)^+$ and

(xi) the following abbreviations are used:

DMSO	dimethyl sulphoxide;
DMF	*N*-dimethylformamide;
DCM	dichloromethane;
THF	tetrahdydrofuran;
DIPEA	*N*,*N*-diisopropylethylamine;
NMP	*N*-methylpyrrolidinone;
HATU	O-(7-Azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate;
Boc	tert-butoxycarbonyl
MeOH	methanol;

EtOH	ethanol; and
EtOAc	ethyl acetate.

EXAMPLE 1

This Example illustrates the preparation of *N*-[1-(3,3-diphenylpropyl)-4-piperidinyl]-*N*-methylisonicotinamide (Compound No. 1 of Table I).

To a solution of isonicotinic acid (0.6mg, 5μM) in NMP (50μL) was added a solution of 4-methylamino-1-(3,3-diphenylpropyl)piperidine dihydrochloride (Method A) (1.9mg, 5μM) and diisopropylethylamine (8μL, 45μM) in NMP (50μL) followed by a solution of bromo-*tris*-pyrrolidinophosphonium hexafluorophosphate (4.7mg, 10μM) in NMP (100μL). After 15h the reaction mixture was concentrated to give the title compound which was characterised by LCMS; MS: 415.

The method of Example 1 can be repeated using different acids in place of isonicotinic acid, or different piperidines (such as 4-methylamino-1-(3-**R**/**S**-phenylbutyl)piperidine dihydrochloride (Method B), 4-propargylamino-1-(3-**R**/**S**-phenylbutyl)piperidine (Method C), 4-allylamino-1-(3,3-diphenylpropyl)piperidine (Method D), 4-allylamino-1-(3-**R**/**S**-phenylbutyl)piperidine (Method E) or 4-(cyclopropylmethyl)amino-1-(3-**R**/**S**-phenylbutyl)piperidine (Method R)) in place of 4-methylamino-1-(3,3-diphenylpropyl)piperidine dihydrochloride.

EXAMPLE 2

This Example illustrates the preparation of *N'*-(2,4-difluorophenyl)-*N*-[1-(2,6-dimethoxybenzyl)piperidin-4-yl]-*N*-phenethylurea (Compound No. 1 of Table III).

To a solution of 2,6-dimethoxybenzaldehyde (1.7mg, 10μM) in NMP (100μL) was added a solution of 4-piperidinyl-*N*-(2-phenylethyl)-2,4-difluorophenylurea.trifluoroacetic acid (Method F) (2.4mg, 5μM) and diisopropylethylamine (1μL, 5.5μM) in NMP (100μL). After 1.5h a solution of sodium triacetoxyborohydride (2.8mg, 15μM) in acetonitrile: NMP, 1:1 (100μL) was added. After 16h at room temperature the reaction mixture was concentrated to give the title compound which was characterised by LCMS; MS: 510.

The procedure described in Example 2 can be repeated using different aldehydes in place of 2,6-dimethoxybenzaldehyde or other piperidines (such as 4-methylamino-1-(3,3-diphenylpropyl)piperidine.dihydrochloric acid (Method A) or 4-amino-1-(3,3-diphenylpropyl)piperidine.ditrifluoroacetic acid (Method G)) in place of 4-piperidinyl-*N*-(2-phenylethyl)-2,4-difluorophenylurea trifluoroacetic acid.

EXAMPLE 3

This Example illustrates the preparation of *N*-[1-(3,3-diphenylpropyl)-piperidin4-yl]-*N*-methyl-2-(trifluoromethoxy)benzenesulphonamide (Compound No. 53 of Table I).

To a solution of 2-trifluoromethoxybenzenesulphonyl chloride (1.3mg, 5μM) in acetonitrile (50μL) was added a solution of 4-methylamino-1-(3,3-diphenylpropyl)-piperidine.dihydrochloride (Method A) (1.9mg, 5μM) and *N*,*N*-diisopropylethylamine (1.8μL, 10μM) in pyridine (50μL). After 15h the reaction mixture was concentrated to give the title compound which was characterised by LCMS; MS: 533.

The procedure described in Example 3 can be repeated using different sulphonylchlorides (such as 4-acetamido,3-chlorobenzenesulphonyl chloride) in place of 2-trifluoromethoxybenzenesulphonyl chloride or different piperidines (such as 4-amino-1-(3,3-diphenylpropyl)piperidine.ditrifluoroacetic acid (Method G)) in place of 4-methylamino-1-(3,3-diphenylpropyl)piperidine dihydrochloride.

EXAMPLE 4

This Example illustrates the preparation of *N'*-(3,4-dichlorophenyl)-*N*-[1-(3,3-diphenylpropyl)piperidin-4-yl]-*N*-methylurea (Compound No. 68 of Table I).

A solution of 4-methylamino-1-(3,3-diphenylpropyl)piperidine.dihydrochloride (Method A) (1.9mg, 5μM) and DIPEA (1.8μL, 10μM) in DCM (100μL) was added to 3,4-dichlorophenylisocyanate (19mg, 0.1mM). After 15h DCM (800μL) was added and Argonaut™ PS-*tris*-amine scavenger resin (0.66g) was added and the reaction mixture agitated. The resin swelled considerably and the mixture was left to stand in order for the DCM to evaporate. Methanol (0.5ml) was added and the mixture agitated; the organic layer

was then transferred to another vessel and concentrated to give the title compound as an oil, which was characterised by LCMS; MS: 496.

The procedure described in Example 4 can be repeated using various isocyanates or carbamoyl chlorides in place of 3,4-dichlorophenylisocyanate or other piperidines (such as 4-amino-1-(3,3-diphenylpropyl)piperidine.ditrifluoroacetic acid (Method G), 4-amino-1-(3-**R/S**-phenylbutyl)piperidine ditrifluoroacetic acid salt (Method H)) in place of 4-methylamino-1-(3,3-diphenylpropyl)piperidine dihydrochloride.

EXAMPLE 5

This Example illustrates the preparation of *N*-[1-(3,3-diphenylpropyl)-piperidin-4-yl]-*N*-methylthiophene-2-carboxamide (Compound No. 96 of Table I).

A solution of 4-methylamino-1-(3,3-diphenylpropyl)piperidine (the free base of the compound described in Method A) (0.1g, 0.32mmol) in dichloromethane (4.0 ml) was added to 2-thiophene carboxylic acid (1.0mmol). To the resulting mixture was added a solution of diisopropylcarbodiimide (0.15ml, 1.0mmol) in dichloromethane (1.0ml) followed by a solution of 1-hydroxybenzotriazole (0.135g, 1.0mmol) in DMF (2.0ml) and the resulting mixture stirred at ambient temperature for 18 hours. The reaction mixture was then applied to an ISOLUTE™ SCX column (5g) which was then washed with MeOH (30ml) followed by a 1:4 mixture of aqueous ammonia and methanol (30ml). Evaporation of the final wash gave the title compound as an oil (101mg, 75% yield); MS: 419.

The procedure described in Example 5 can be repeated using different carboxylic acids in place of 2-thiophene carboxylic acid or other piperidines (such as 4-amino-1-(3,3-diphenylpropyl)piperidine (free base from Method G), 4-methylamino-1-(3-**R/S**-phenylbutyl)piperidine (free base from Method B) or 4-amino-1-(3-**R/S**-phenylbutyl)piperidine (free base from Method H)) in place of 4-methylamino-1-(3,3-diphenylpropyl)piperidine.

EXAMPLE 6

This Example illustrates the preparation of *N*-[1-(3,3-diphenylpropyl)-4-piperidinyl]-(*N*-methyl)-3-chlorophenylurea (Compound 144 of Table I).

A solution of 4-methylamino-1-(3,3-diphenylpropyl)piperidine (the free base of the compound described in Method A) (0.1g; 0.32mmol) in DCM (4.0 ml) was added to 3-chlorophenyl isocyanate (1.0mmol). The resulting mixture was stirred at ambient temperature for 18 hours. The reaction mixture was then applied to an ISOLUTE™ SCX column (5g) which was then washed with methanol (30ml) followed by a 1:4 mixture of aqueous ammonia and MeOH (30ml). Evaporation of the final wash gave the product as an oil (112mg, 76% yield); MS: 462.

The procedure described in Example 6 can be repeated using different isocyanates or carbamoyl chlorides in place of 3-chlorophenylisocyanate or other piperidines (such as 4-methylamino-1-(3-**R/S**-phenylbutyl)piperidine (free base from Method B)) in place of 4-methylamino-1-(3,3-diphenylpropyl)piperidine.

EXAMPLE 7

This Example illustrates the preparation of *N*-[1-(3,3-diphenylpropyl)-4-piperidinyl]-*N*-methyl-4-(phenylmethoxy)phenylacetamide (Compound No. 268 of Table I).

To a solution of 4-methoxyphenylacetic acid (0.8mg, 5μmol) in NMP (50μL) was added a solution of 4-methylamino-1-(3,3-diphenylpropyl)piperidine dihydrochloride (Method A) (1.9mg, 5μmol) and DIPEA (8μL, 45μmol) in NMP (50μL) followed by a solution of bromo-*tris*-pyrrolidino-phosphonium hexafluorophosphate (4.7mg, 10μmol) in NMP (100μL). After 15h the reaction mixture was concentrated to give the title compound which was characterised by LCMS; MS: 533.

EXAMPLE 8

This Example illustrates the preparation of *N*-[1-(3,3-diphenylpropyl)-4-piperidinyl]-*N*-allyl-4-fluorophenylacetamide (Compound No. 269 of Table I).

To 4-fluorophenylacetic acid (1mmol) was added 4-allylamino-1-(3,3-diphenylpropyl)piperidine (0.1g; 0.3mmol) in dichloromethane (2ml). A solution of 1-hydroxybenztriazole (0.135g; 0.1mmol) in DMF (2ml) and di-isopropyl-carbodiimide (0.126ml; 1mmol) in DCM was then added. The resulting mixture was stirred at room temperature overnight. The mixture was then applied to an ISOLUTE™ SCX cartridge (5g) and washed with methanol (30ml). The product was then eluted with 15% methylamine in ethanol. Purification was achieved by BondElut chromatography eluting with a solvent

mixture of DCM to 5% methanol in DCM yielding the title compound (72mg, 50%), which was characterised by LCMS; MS: 471.

EXAMPLE 9

This Example illustrates the preparation of *N*-[1-(3,3-diphenylpropyl)-4-piperidinyl]-*N*-ethyl-4-trifluoromethoxyphenylacetamide (Compound No. 282 of Table I).

To a solution of 4-trifluoromethoxyphenylacetic acid (188mg, 0.92mmol) in dichloromethane (2ml) was added 1-hydroxybenztriazole (124mg) followed by diisopropylcarbodiimide (0.14ml) and DMF (1ml). The mixture was stirred at room temperature for 1h, then a solution of 4-ethylamino-1-(3,3-diphenylpropyl)piperidine (147mg, 0.46mmol) in dichloromethane (2ml) was added. The resulting mixture was stirred overnight then purified by eluting through an ISOLUTE™ SCX column with methanol followed by 2% aqueous ammonia in methanol. The product was then dissolved in ethyl acetate (2 ml) and treated with 1M HCl in diethyl ether (4 ml) giving the hydrochloride salt which was isolated by filtration, yielding *N*-[1-(3,3-diphenylpropyl)-4-piperidinyl]-*N*-ethyl-4-trifluoromethoxyphenylacetamide hydrochloride as a foam, 210mg, 87%; NMR: 1.1 (m ,3H), 1.7 (m, 2H), 2.1 (m, 2H), 3.0 (m, 4H), 3.5 (m, 5H), 3.8 (m, 4H), 4.3 (m, 1H), 7.1 (m, 2H), 7.3 (m, 12H); MS: 525.

EXAMPLE 10

This Example illustrates the preparation of *N'*-(4-fluorophenylmethyl)-*N*-[1-(3,3-diphenylpropyl)-4-piperidinyl]-*N*-methylurea (Compound No. 388 of Table I).

To 4-fluorophenyl isocyanate (0.75mmol) was added a solution of 4-methylamino-1-(3,3-diphenylpropyl)piperidine (0.19g; 0.5mmol) in DCM (4ml). The resulting mixture was stirred at room temperature overnight. The resulting reaction mixture was then applied to an ISOLUTE™ SCX cartridge (5g) and washed with methanol (30ml). The product was then eluted using a 4:1 mixture of methanol and aqueous ammonia. Purification was achieved by BondElut chromatography eluting with a solvent mixture of DCM to 5% methanol in DCM to give the title compound (26 mg, 11%) which was characterised by LCMS; MS: 446.

EXAMPLE 11

This Example illustrates the preparation of *N'*-(2,4-difluorophenyl)-*N*-[1-(3,3-diphenylpropyl)-4-piperidinyl]-*N*-phenethylurea (Compound No. 314 of Table I).

To a solution of *N'*-(2,4-difluorophenyl)-*N*-(4-piperidinyl)-*N*-phenethylurea trifluoroacetic acid salt (300mg, 0.63mmol) in DMF (5ml) was added 3,3-diphenyl-1-

bromopropane (360mg, 1.26mmol) followed by DIPEA (0.442ml, 2.52mmol). The resulting mixture was stirred at room temperature for 24h. The reaction mixture was partitioned between water and dichloromethane, the organic phase was washed with water, dried ($MgSO_4$) and concentrated. The residue was purified by eluting through a silica gel cartridge with ethyl acetate followed by 5% ethanol in ethyl acetate to give the title compound as a gum, 80mg; NMR: 1.6 (m, 6H), 4.9 (m, 5H), 2.2 (m, 3H), 2.8 (m, 3H), 3.9 (m, 2H), 7.0 (m, 1H), 7.2 (m, 15H), 7.4 (m, 1H), 8.0 (s, 1H); MS: 554.

EXAMPLE 12

This Example illustrates the preparation of *N'*-(4-trifluoromethylphenylmethyl)-*N*-[1-(3,3-diphenylpropyl)-4-piperidinyl]-*N*-ethylurea (Compound No. 323 of Table I).

A solution of 4-trifluoromethylphenylacetic acid (0.8mmol) in dry THF (2.0ml) was cooled to 0°C and triethylamine (0.11ml; 0.8mmol) in THF (1.0ml) and diphenylphosphorylazide (0.17ml; 0.8mmol) in THF (2ml) were added. Stirring was continued for 30min. The mixture was allowed to warm to ambient temperature before toluene (5ml) was added and the mixture heated to 100°C for 1h. After cooling to room temperature, a solution of 4-ethylamino-1-(3,3-diphenylpropyl)piperidine (0.2g; 0.6mmol) in ethyl acetate (2ml) was added and the mixture allowed to stir at room temperature for 72h. The reaction mixture was then washed with aq. $NaHCO_3$ solution, dried and evaporated. Purification was by passage through a BondElut cartridge (Si) eluting with a gradient from 0 - 5% methanol in DCM, yielding the title compound (153mg, 49%) which was characterised by LCMS; MS: 524.

EXAMPLE 13

This Example illustrates the preparation of pyrrolidine carboxylic acid *N*-[1-(3,3-diphenylpropyl)-4-piperidinyl]-*N*-methyl amide (Compound No. 391 of Table I).

To diethylcarbamoyl chloride (0.75mmol) was added a solution of 4-methylamino-1-(3,3-diphenylpropyl)piperidine (0.19g; 0.5mmol) in DCM (4ml) followed by triethylamine (0.14ml; 1mmol). The resulting mixture was stirred at room temperature overnight. The resulting reation mixture was then applied to an ISOLUTE™ SCX cartridge (5g) and washed with methanol (30ml). The product was then eluted using a 4:1 mixture of methanol and 0.88 aqueous ammonia. Purification was achieved by BondElut chromatography eluting with a solvent mixture of DCM to 5% methanol in DCM to give the product (79 mg, 39%) which was characterised by LCMS; MS: 406.

EXAMPLE 14

This Example illustrates the preparation of *N*-[1-(3,3-diphenylpropyl)-4-piperidinyl]-*N*-methyl-4-(cyclopropylaminosulfonyl)phenylacetamide (Compound No. 354 of Table I).

N-[1-(3,3-Diphenylpropyl)-4-piperidinyl]-*N*-methyl-4-fluorosulfonylphenyl-acetamide (0.005mmol, in 100μL MeCN) and cyclopropylamine (0.01mmol in 100μL MeCN) were mixed and allowed to stand overnight. The solvent was then evaporated to dryness under Genevac high vacuum.

EXAMPLE 15

This Example illustrates the preparation of *N*-[1-(3,3-diphenylpropyl)-4-piperidinyl]-*N*-methyl-4-(2-hydroxyethylaminocarbonyl)phenylacetamide hydrochloride (Compound No. 385 of Table I).

A mixture of *N*-[1-(3,3-diphenylpropyl)-4-piperidinyl]-*N*-methyl-4-methoxycarbonylphenylacetamide (0.1g; 0.2mmol) was heated at 60°C in a mixture of ethanolamine (1.0mL) and acetonitrile (1.0mL) for 12 hours. After cooling the mixture was partitioned between ethyl acetate (5mL) and water (8mL). The organic layer was washed a further twice with water and dried (Na_2SO_4) before purification on a silica BondElut, eluting with a gradient from 5 - 25% methanol in dichloromethane. The purified product was dissolved in ethyl acetate and treated with HCl in diethyl ether before evaporation to give the title compound as a solid (68 mg, 62%) which was characterised by LC-MS; MS: 514.

EXAMPLE 16

This Example illustrates the preparation of 4-(2-[4-methanesulfonylphenyl])-pentenoic acid *N*-[1-(3,3-diphenylpropyl)-4-piperidinyl]amide hydrochloride salt (Compound No. 390 of Table I).

To a cooled (5°C) solution of *N*-[1-(3,3-diphenylpropyl)-4-piperidinyl]-4-methanesulfonylphenylacetamide (1.61g, 3.28mmol) in DMF (15mL) was added sodium hydride (131mg 60% dispersion, 3.6mmol). The resulting mixture was stirred for 5 minutes before the addition of allyl bromide (0.3mL, 3.44mmol). The reaction mixture was stirred at room temperature for 2 h then quenched with water. The mixture was extracted twice with ethyl acetate and the combined organic extracts were washed with water and brine, dried and evaporated. The residue was purified by silica gel chromatography (eluent 3% MeOH in DCM). The crude product was treated with ethereal HCl to afford the title compound (0.902g); NMR ($CDCl_3$): 1.2 (m, 2H), 1.9 (m, 2H), 2.1 (m, 2H), 2.3 (m, 4H), 2.5 (m, 1H), 2.8

(m, 3H), 3.0 (s, 3H), 3.4 (m, 1H), 3.8 (m, 1H), 4.0 (dd, 1H), 5.1 (m, 2H), 5.4 (d, 1H), 5.7 (m, 1H), 7.2 (m, 10H), 7.6 (d, 2H), 7.9 (d, 2H); MS: 531.

EXAMPLE 17

This Example illustrates the preparation of *N'*-phenylmethyl-*N*-[1-(3,3-diphenylpropyl)-4-piperidinyl]-*N*-allylurea (Compound No. 245 of Table II).

3-Phenylbutyraldehyde (0.2g, 1.36mmol) was added to a solution of *N'*-phenylmethyl-*N*-[piperidin-4-yl]-*N*-allylurea hydrochloride (370mg, 1.36mmol) in methanol (20ml). After 15 mins sodium triacetoxyborohydride (430mg, 2.0mmol) was added portionwise over 15mins and the reaction was left to stir for 16h. Water (5ml) was added to the mixture and the methanol was removed *in vacuo*. The solution was diluted with water (30ml), and partitioned with EtOAc (2x40ml). The organic fractions were combined and washed with brine (30ml), dried ($MgSO_4$) and concentrated. The oil was dissolved in MeOH (5ml) and then applied to an ISOLUTE™ SCX column (5g) which was then washed with MeOH (30ml) followed by a 1:4 mixture of aqueous ammonia and methanol (30 ml). Addition of ethereal HCl to the final wash, followed by evaporation gave the title compound as a gum (152mg, 0.38mmol); MS: 406.

EXAMPLE 18

This Example illustrates the preparation of *N*-[1-(3-phenyl-3-[4-fluorophenyl]-3-hydroxypropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 11 of Table III).

To a solution of *N*-[1-(3-[4-fluorophenyl]-3-oxopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide hydrochloride (470mg, 0.92mmol) in THF (40mL) under an inert atmosphere was added phenylmagnesium bromide (10mL, 1M in THF) at room temperature. After stirring for 1h saturated aqueous sodium bicarbonate solution was added and the resulting mixture was extracted with ethyl acetate. The organic phase was dried ($MgSO_4$) and concentrated. The title compound was obtained by silica column chromatography, eluting with 10% methanol in ethyl acetate yielding 120mg. NMR ($CDCl_3$): 1.18 and 1.23 (t, 3H), 1.65 (m, 2H), 1.84 (m, 2H), 2.42 (m, 2H), 3.02 (s, 3H), 3.35 (m, 2H), 3.65 (m, 4H), 3.68 and 3.78 (s, 2H), 4.73 (t, 2H), 6.97 (m, 2H), 7.2-7.4 (m, 9H), 7.90 (d, 2H); MS: 553.

EXAMPLE 19

This Example illustrates the preparation of *N*-[1-(3-phenyl-4-pentenyl)-4-piperidinyl]-*N*-methyl-4-fluorophenylacetamide (Compound No. 12 of Table III).

5-Bromo-3-phenylpent-1-ene (131mg, 0.58mmol), 4-(*N*-(4-fluorophenyl-acetamido)-*N*-methyl)aminopiperidine (73mg, 0.29mmol), potassium carbonate (120mg, 0.87mmol) and tetrabutylammonium iodide (5mg) were stirred in DMF (3ml). After 16h, water was added and the mixture extracted with EtOAc (2x20ml). The organics were combined and washed with water, dried (MgSO4), concentrated and purified by Bond Elut chromatography (eluent DCM, followed by 2.5% EtOH/DCM and finally 5% EtOH/DCM) to afford the title compound as an oil (55mg, 0.14mmol); MS: 395.

EXAMPLE 20

This Example illustrates the preparation of *N*-[1-(3-phenyl-3-azetidinylpropyl)-4-piperidinyl]-*N*-methyl-4-fluorophenylacetamide dihydrochloride (Compound No. 13 of Table III).

To a solution of *N*-[1-(3-phenyl-3-chloropropyl)-4-piperidinyl]-*N*-methyl-4-fluorophenylacetamide (120mg, 0.3mmol) in DCM (5mL) was added azetidine (0.12mL, 1.8mmol) and the resulting mixture was stirred at room temperature for 18h. The reaction mixture was washed with water, dried ($MgSO_4$) concentrated, and purified by Bond Elut chromatography (eluent 5% MeOH/DCM followed by 10% MeOH/DCM) to afford the title compound as an oil which was then treated with ethereal HCl to provide *N*-[1-(3-phenyl-3-azetidinylpropyl)-4-piperidinyl]-*N*-methyl-4-fluorophenylacetamide dihydrochloride as a white solid (35 mg, 24%); NMR (d6-DMSO, 373K): 1.5-1.65 (m, 2H), 1.85-2.1 (m, 4H), 2.55-2.9 (m, 8H), 3.1-3.2 (m, 1H), 3.25-3.35 (m, 1H), 3.6-3.75 (m, 5H), 4.1-4.2 (m, 2H), 7.0-7.1 (m, 2H), 7.2-7.3 (m, 2H), 7.35-7.5 (m, 5H); MS: 424.

EXAMPLE 21

This Example illustrates the preparation of *N*-[1-(3-phenyl-3-[4-fluorophenyl]propyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 15 of Table III).

To a solution of 4-(*N*-(4-fluorophenylacetamido)-*N*-methyl)aminopiperidine (143mg, 1.74mmol) in DMF (5mL) was added 3-phenyl-3-(4-fluorophenyl)-1-bromopropane (Method V) (420mg, 1.5mmol) and K_2CO_3 (300mg). The reaction was then stirred overnight and poured onto water (20mL). Extracted into EtOAc, washed with water (20mL), brine (20mL), and dried over $MgSO_4$. The solvents were evaporated and the crude product was purified by

Bond Elut chromatography (eluent 5% MeOH/DCM) to afford the title compound as a sticky gum, (148mg, 20%); NMR: 1.65 (2H, m), 2.20 (1H, broad t), 3.2-2.6 (9H, m), 3.8-3.6 (6H, m), 4.10 (1H, m) and 7.4-7.2 (13H, m); MS: 463.

EXAMPLE 22

This Example illustrates the preparation of *N*-[1-(3,3-di-[4-fluorophenyl]propyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 16 of Table III).

To a DMF solution of 1-(3,3-di-(4-fluorophenyl)propyl)-4-(methylamino)piperidine (250mg, 0.72mmol, in 5mL) was added 4-fluorophenylacetic acid (115mg, 0.75mmol), HATU (285mg, 0.75mmol), and DIPEA (130µl). The reaction was stirred overnight and poured into water (20mL). The organics were extracted into EtOAc (20mL) and dried over $MgSO_4$. The desired product was then precipitated from the EtOAc by addition of 2M HCl in Et_2O, to afford a pale yellow gum (139mg, 46%); NMR: 1.60 (2H, m), 2.20 (2H, m), 2.75 (3H, s), 3.3-3.7 (12H, m), 6.80 (2H, m) and 7.3-7.0 (10H, m); MS: 481.

EXAMPLE 23

This Example illustrates the preparation of *N*-[1-(*N*,*N*-diphenyl-2-ethylamino)-4-piperidinyl]-*N*-allyl-4-methanesulfonylphenylacetamide (Compound No. 18 of Table III).

To a mixture of *N*-(4-piperidinyl)-*N*-allyl-4-methanesulfonylphenylacetamide (0.25g, 0.74mmol) and 4-methyl-2-pentanone (10mL) was added potassium carbonate (0.31g), potassium iodide (100mg) and *N*-(2-bromoethyl)diphenylamine (0.21g) and the resulting mixture was stirred and heated to reflux for 18 h. After cooling, water was added and the volatiles removed by evaporation. The residue was extracted three times with ethyl acetate and the combined extracts were dried and concentrated to give an oil which was purified by eluting through a silica gel column with 1% methanol in dichloromethane then 5% methanol in dichloromethane to give the title compound (73mg); NMR: 1.5 (m, 4H), 2.1 (m, 2H), 2.5 (m, 2H), 3.1 (s, 3H), 3.8 (m, 7H), 3.9 (s, 2H), 5.1 (m, 2H), 5.8 (m, 1H), 6.9 (m, 6H), 7.2 (m, 4H), 7.4 (d, 2H), 7.8 (d, 2H); MS: 532.

EXAMPLE 24

This Example illustrates the preparation of *N*-[1-(*N*-phenyl-*N*-[2-(4-hydroxyphenyl)ethylcarbonyl]-2-ethylamino)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 20 of Table III).

To 3-(4-hydroxyphenyl)propanoic acid (0.1mmol) was added DMF (5µL) followed by oxalyl chloride (1mL of a 0.1M solution in DCM, 0.1mmol) and the resulting mixture was

shaken at room temperature for 2h. 100μL Of this mixture was then added to 100μL of a solution of *N*-[1-(*N*-phenyl-2-ethylamino)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (230mg, 0. mmol) and triethylamine (0.334mL, 2.4mmol) in DCM (12mL). The resulting mixture left at room temperature for 20 h then water (250μL) and DCM (250μL) were added and the mixture was shaken. The aqueous phase was removed and the organic phase was concentrated giving the title compound which was characterised by LC-MS; MS: 591.

EXAMPLE 25

This Example illustrates the preparation of *N*-[1-(3-phenyl-3-aminopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide dihydrochloride (Compound No. 23 of Table III).

To a solution of 3-phenyl-3-Bocaminopropanal (513mg, 2.0mmol) and *N*-(4-piperidinyl)-*N*-ethyl-4-methanesulfonylphenylacetamide (645mg, 2.0mmol) in methanol (15mL) was added acetic acid (0.2mL) and the resulting mixture was stirred at room temperature for 1 h. Sodium triacetoxyborohydride (844mg, 4.0mmol) was added and the mixture was stirred at room temperature for 18 h then evaporated. The residue was partitioned between DCM and water, and the organic phase was washed with brine, dried and concentrated. The residue was suspended in 4M HCl in dioxane (20mL) and methanol (5mL) was added. The resulting mixture was heated to reflux for 7 h, then cooled to room temperature and concentrated giving an oily residue which was purified by silica gel chromatography (eluent 5% MeOH /DCM then 10% MeOH/DCM) yielding the title compound as a solid (675 mg); NMR (d6 DMSO at 373K): 1.1 (t, 3H), 1.5 (m, 2H), 1.9 (m, 2H), 2.0 (m, 1H), 2.3 (m, 2H), 3.0 (m, 1H), 3.2 (m, 4H), 3.3 (q, 2H), 3.9 (s, 2H), 4.0 (m, 1H), 4.4 (m, 1H), 7.4 (m, 3H), 7.5 (m, 4H), 7.9 (m, 2H); MS: 458.

EXAMPLE 26

This Example illustrates the preparation of *N*-[1-(3-phenyl-3-benzoylaminopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 1 of Table IV).

A solution of benzoic acid (0.005mmol) in NMP (50μL) was added to a solution of HATU (0.01mmol) and diisopropylethylamine (0.03mmol) in NMP (100μL). To the resulting mixture was added *N*-[1-(3-phenyl-3-aminopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide dihydrochloride (Example 25; 0.005mmol) in NMP (100μL). The mixture was left at room temperature for 18 h, then evaporated. The residue

was partitioned between DCM (250μL) and water (250μL) and the phases separated. The organic phase was concentrated giving the title compound which was characterised by LC-MS; MS: 562.

EXAMPLE 27

This Example illustrates the preparation of *N*-[1-(*N*-Phenyl-2-ethylamino)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 24 of Table III).

To a mixture of *N*-(4-piperidinyl)-*N*-ethyl-4-methanesulfonylphenylacetamide (2.0 g, 6.2 mmol) and *N*-(2-chloroethyl)aniline hydrochloride (1.2 g, 6.2 mmol) (J. Med. Chem. **1965**, 173) in 4-methyl-2-pentanone (15 mL) was added potassium carbonate (2.56 g, 18.6 mmol) and potassium iodide (150 mg, 0.9 mmol) and the resulting mixture stirred at reflux for 20 h. After cooling to room temperature the solid was removed by filtration and the filtrate concentrated. The residue was purified by Bond Elut chromatography (eluent 5% MeOH/DCM) to afford, after trituration with diethyl ether, the title compound as a white solid (1.30 g, 50%); NMR (d6 DMSO, 373K): 1.1 (t, 3H), 1.4 (m, 2H), 1.8 (m, 2H), 2.1 (m, 2H), 2.5 (m, 2H), 3.1 (m, 5H), 3.3 (q, 2H), 3.8 (s, 2H), 5.0 (m, 1H), 6.6 (m, 3H), 7.1 (dd, 2H), 7.5 (d, 2H), 7.8 (d, 2H); MS: 444.

Compound No. 25 of Table III was prepared according to the method of Example 27 using *N*-(4-piperidinyl)-N-ethyl-4-fluorophenylacetamide. NMR: 1.0 and 1.5 (t, 3H), 1.3 (m, 1H) 1.5 (m, 1H), 1.7 (m, 2H), 2.0 (m, 2H), 2.4 (m, 2H), 2.9 (m, 2H), 3.1 (m, 2H), 3.2 (m, 2H), 3.6 and 3.7 (s, 2H), 4.1 (m, 1H), 5.2 (br s, 1H), 6.5 (m, 3H), 7.0 (dd, 2H), 7.1 (dd, 2H), 7.2 (m, 2H); MS: 384.

EXAMPLE 28

This Example illustrates the preparation of Compound No. 26 of Table III.

To a solution of *N*-[1-(3-phenyl]-3-oxopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide hydrochloride (5.00g, 10.1mmol) in methanol (150mL) was added sodium borohydride (0.96g, 25.4mmol) portionwise. The resulting mixture was stirred at room temperature for 20h. Water (10mL) was added and the mixture was evaporated. The residue was purified by silica column chromatography (gradient elution from ethyl acetate to 50% ethyl acetate/MeOH) to give the title compound (3.92g, 84%); NMR: ($CDCl_3$): 1.14 and 1.23 (t, 3H), 1.56 (m, 1H), 1.75 (m, 2H), 1.83 (m, 3H), 1.98 (m, 1H), 2.20 (m, 1H), 2.56 (m,

1H), 2.66 (m, 1H), 3.02 (s, 3H), 3.10 (m, 1H), 3.18 (m, 1H), 3.31 (q, 2H), 3.57 and 4.49 (m, 1H), 3.79 and 3.80 (s, 2H), 4.94 (m, 1H), 7.23 (m, 1H), 7.34 (m, 4H), 7.44 (d, 2H) and 7.90 (d, 2H); MS: 459.

EXAMPLE 29

This Example illustrates the preparation of *N*-[1-(4,4-diphenyl-but-2-yl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide hydrochloride (Compound No. 27 of Table III).

N-(4-Piperidinyl)-*N*-ethyl-4-methanesulfonylphenylacetamide (323mg, 1mmol) was dissolved in DCM (10ml). Acetic acid (1ml) and 4,4-diphenyl-2-butanone (384mg, 1.5mmol) was added followed by sodium triacetoxyborohydride (516mg, 2.1mmol). The reaction mixture was stirred at room temperature for 7 days. Water (10ml) was added and the layers separated. The organic phase was washed with brine, dried ($MgSO_4$) and evaporated to dryness. The residue was purified by Bond Elut chromatography (eluent 5% MeOH/DCM). The resultant oily residue was dissolved in a small amount of DCM, 1M HCl in diethyl ether was added and the mixture concentrated to yield the title compound as a white solid (120mg, 22%); NMR (d6-DMSO, 373K): 1.0-1.2 (m, 6H), 1.5- 2.1 (m, 6H), 2.5 - 3.0 (m, 6H), 3.1 (s, 3H), 3.3 (q, 2H), 3.8 (s, 2Hs), 4.1 (t, 1H) 7.1 (m, 2H), 7.2-7.4 (m, 8H), 7.5 (d, 2H), 7.9 (d, 2H); MS: 533.

EXAMPLE 30

This Example illustrates the preparation of *N*-[1-(4-phenyl-but-2-yl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 28 of Table III).

To a mixture of *N*-(4-piperidinyl)-*N*-ethyl-4-methanesulfonylphenylacetamide (324mg, 1mmol), 4-phenyl-2-butanone (0.22ml, 1.5mmol), sodium triacetoxyborohydride (318mg, 1.5mmol) and acetic acid (0.11ml, 2mmol) in DCM (8ml) was added a little $MgSO_4$ and the resulting mixture heated to reflux for 48h. The reaction mixture was eluted through a column of silica gel (isohexane then 89%DCM/10%MeOH/1%NH_4OH) yielding the title compound (60mg); NMR ($CDCl_3$): 1.1 and 1.2 (t, 3H), 1.3 (t, 3H), 1.6 (br m, 2H), 1.8 (m, 1H), 2.0 (s, 2H), 2.1 (m, 2H), 2.6 (br m, 3H), 3.0 (s, 3H), 3.2 (br m, 2H), 3.3 (q, 2H), 3.8 (s, 2H), 4.5 (m, 1H), 7.2 (m, 3H), 7.3 (m, 2H), 7.4 (m, 2H) and 7.9 (m, 2H); MS: 457.

EXAMPLE 31

This Example illustrates the preparation of *N*-[1-(3-[3-trifluoromethylphenyl]-butyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 29 of Table III).

To a solution of *N*-(4-piperidinyl)-*N*-ethyl-4-methanesulfonylphenylacetamide (680mg, 2.1mmol) in MeOH/DCM (10ml, 1:1) was added 3-(3-trifluoromethylphenyl)butyraldehyde (Method BP) (500mg, 2.3mmol) and acetic acid (0.25ml). The resulting mixture was stirred at room temperature for 30min. then sodium triacetoxyborohydride (735mg, 3.2mmol) was added. The resulting mixture was stirred at room temperature for 2h then quenched with water (5ml) and concentrated to a third of the volume. The residual mixture was extracted with DCM and the organic extracts washed with saturated $NaHCO_3$ solution and brine and evaporated to give the title compound (260mg); NMR ($CDCl_3$): 1.18 (t, 3H), 1.3 (t, 3H), 1.5 (m, 1H), 1.7 (m, 6H), 2.0 (m, 2H), 2.2 (m, 2H), 2.8 (m, 3H), 3.05 (s, 3H), 3.3 (m, 2H), 3.8 (d, 2H), 7.4 (m, 6H), 7.9 (d, 2H); NMR: 525.

Compound No. 30 of Table III: NMR ($CDCl_3$): 1.18 (t, 3H), 1.3 (t, 3H), 1.5 (m, 1H), 1.7 (m, 8H), 2.2 (m,2H), 2.7 (m, 1H), 2.9 (m, 2H), 3.05 (s, 3H), 3.3 (q, 2H), 3.8 (d, 2H), 7.05 (d, 1H), 7.2 (m, 3H), 7.45 (m,2H), 7.9 (d,2H); MS: 491.

Compound No. 31 of Table III: NMR ($CDCl_3$): 1.18 (t, 3H), 1.3 (t, 3H), 1.5 (m, 1H), 1.7 (m, 8H), 2.2 (m, 2H), 2.7 (m, 1H), 2.9 (m, 2H), 3.05 (s, 3H), 3.3 (q, 2H), 3.8 (d, 2H), 7.2 (d, 3H), 7.3 (m, 2H), 7.45 (m,2H), 7.9 (d, 2H); MS: 457.

Compound No. 32 of Table III: NMR ($CDCl_3$): 1.18 (t, 3H), 1.3 (t, 3H), 1.5 (m, 1H), 1.7 (m, 8H), 2.2 (m, 2H), 2.7 (m, 1H), 2.9(m, 2H), 3.05 (s, 3H), 3.3 (q, 2H), 3.8 (d, 2H), 7.0 (d, 1H) 7.35 (d, 1H), 7.45 (d, 2H), 7.9 (d, 2H); MS: 525.

EXAMPLE 32

This Example illustrates the preparation of *N*-[1-(3,3-diphenylpropyl)-3-pyrrolidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 33 of Table III).

To a solution of 4-methanesulfonylphenylacetic acid (1.01g, 4.72mmol) in DCM (20ml) was added carbonyldiimidazole (765mg, 4.72mmol) and the resulting mixture stirred at room temperature for 2h. A solution of 3-amino-1-(3,3-diphenylpropyl)pyrrolidine di-

(trifluoroacetic acid) salt (Method BQ) (2.4g, 4.72mmol) and triethylamine (1.43g, 11.4mmol) in DCM (10ml) was added and the resulting mixture stirred at room temperature for 2h. The mixture was washed twice with water (50ml), dried and evaporated. The residue was purified by silica column chromatography (eluent DCM then ethyl acetate) giving the title compound (1.6g); NMR: 1.5 (m, 1H), 2-2.2 (m, 6H), 2.6 (m, 2H), 3.5 (s, 2H), 3.95 (t, 1H), 4.1(m, 2H),7.1-7.3 (m 10H), 7.5(d, 2H), 7.8(d, 2H), 8.3 (d, 1H); MS: 477.

EXAMPLE 33

This Example illustrates the preparation of *N*-[1-(3-[4-chlorophenyl]-3-[4-pyridyl]propyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 34 of Table III).

N-(4-Piperidinyl)-*N*-ethyl-4-methanesulfonylphenylacetamide (480mg, 1.47mmol) was dissolved in DCM (40ml). Acetic acid (6ml) and 3-(4-chlorophenyl)-3-(4-pyridyl)propionaldehyde (Method BR) (2.2mmol) was added and the mixture stirred at room temperature for 30min. followed by the addition of sodium triacetoxyborohydride (340mg, 1.6mmol). The reaction mixture was stirred at room temperature for 2h. The reaction mixture was eluted through a column of silica gel (ethyl acetate then 89%DCM/ 10%MeOH/ 1%NH_4OH) yielding the title compound (60mg); NMR ($CDCl_3$): 1.1 and 1.3 (t, 3H), 1.5 (br m, 1H), 1.8 (m, 4H), 2.2 (m, 4H), 2.9 (m, 2H), 3.0 (s, 3H), 3.3 (q, 2H), 3.5 (br m, 1H), 3.8 (m, 2H), 4.0 (m, 1H), 4.4 (br m, 1H), 7.1 (m, 4H), 7.3 (m, 2H), 7.5 (m, 2H), 7.9 (m, 2H) and 8.5 (m, 2H); MS: 554.

Compound No in Table III	^{1}H NMR ($CDCl_3$)
35	1.1 and 1.3 (t, 3H), 1.5 (m, 1H), 1.7 (br m, 4H), 2.0 (m, 1H), 2.2 (m, 3H), 2.4 (m, 1H), 2.9 (m, 2H), 3.0 (s, 3H), 3.3 (q, 2H), 3.8 (m, 2H), 4.1 (m, 1H), 4.4 (m, 1H), 7.1 (m, 2H), 7.2 (m, 4H), 7.4 (m, 2H), 7.6 (t, 1H), 7.9 (d, 2H) and 8.5 (m, 1H)
36	1.1 and 1.2 (t, 3H), 1.5 (br m, 1H), 1.7 (br m, 4H), 2.0 (m, 1H), 2.2 (m, 2H), 2.3 (m, 2H), 2.4 (m, 1H), 2.9 (m, 2H), 3.0 (s, 3H), 3.3 (q, 2H), 3.5 (m, 1H), 3.8 (m, 2H), 3.9 (t, 1H), 4.4 (m, 1H), 5.9 (s, 2H), 6.7 (s, 2H), 7.2 (m, 4H), 7.4 (m, 2H) and 7.9 (d, 2H)

37	1.1 and 1.2 (t, 3H), 1.4 (m, 1H), 1.7 (m, 2H), 1.8 (m, 2H), 2.0 (br t, 1H), 2.2 (m, 2H), 2.4 (d, 1H), 2.9 (m, 2H), 3.0 (s, 3H), 3.3 (m, 2H), 3.5 (m, 1H), 3.8 (m, 2H), 3.9 (m, 1H), 4.4 (m, 1H), 7.2 (m, 9H), 7.4 (m, 2H) and 7.9 (d, 2H)
38	1.1 and 1.2 (t, 3H), 1.7 (br m, 4H), 2.0 (m, 1H), 2.2 (m, 2H), 2.4 (m, 1H), 2.9 (m, 2H), 3.0 (s, 3H), 3.3 (m, 2H), 3.5 (m, 1H), 3.6 (m, 1H), 3.8 (m, 2H), 4.0 (m, 1H), 4.4 (m, 1H), 7.3 (m, 10H) and 7.9 (d, 2H)
39	1.1 and 1.2 (t, 3H), 1.4 (m, 1H), 1.7 (m, 2H), 1.8 (m, 2H), 2.0 (br t, 1H), 2.2 (m, 3H), 2.9 (m, 2H), 3.0 (s, 3H), 3.3 (m, 2H), 3.5 (m, 1H), 3.6 and 4.5 (m, 1H), 3.8 (m, 5H), 3.9 (t, 1H), 6.8 (d, 2H), 7.2 (m, 7H), 7.4 (m, 2H) and 7.9 (d, 2H)
40	1.1 and 1.2 (t, 3H), 1.5 (m, 1H), 1.7 (m, 2H), 1.8 (m, 2H), 2.2 (m, 3H), 2.4 (m, 1H), 2.9 (m, 2H), 3.0 (s, 3H), 3.3 (m, 2H), 3.5 (m, 1H), 3.8 (m, 2H), 4.0 (br t, 1H), 4.4 (m, 1H), 7.2 (m, 9H), 7.4 (m,2H) and 7.9 (d,2H)
41	1.1 and 1.2 (t, 3H), 1.5 (m, 1H), 1.7 (m, 2H), 1.8 (m, 2H), 2.0 (br t, 1H), 2.2 (m, 3H), 2.3 (s, 3H), 2.9 (m, 2H), 3.0 (s, 3H), 3.3 (m, 2H), 3.5 (m, 1H), 3.6 and 4.4 (m, 1H), 3.8 (m, 2H), 3.9 (t, 1H), 7.1 (m, 5H), 7.2 (m, 4H), 7.4 (m, 2H) and 7.9 (d, 2H)
42	1.1 and 1.3 (t, 3H), 1.5 (m, 1H), 1.7 (m, 4H), 2.0 (br t, 1H), 2.2 (m, 3H), 2.4 (m, 1H), 2.9 (m, 2H), 3.0 (s, 3H), 3.3 (m, 2H), 3.6 (br m, 2H), 3.8 (m, 2H), 4.0 (m, 1H), 4.4 (m, 1H), 7.3 (m, 11H) and 7.9 (d, 2H)
43	1.1 and 1.3 (t, 3H), 1.5 (m, 2H), 1.7 (m, 4H), 1.9 (m, 2H), 2.2 (m, 2H), 2.9 (m, 1H), 3.0 (s, 3H), 3.1 (m, 1H), 3.4 (m, 2H), 3.8 (m, 2H), 4.0 (t, 1H), 4.4 (m, 1H), 7.0 (m, 4H), 7.2 (m, 4H), 7.4 (d, 2H) and 7.9 (d, 2H).
44	1.6 (m, 4H), 2.0 (m, 2H), 2.2 (m, 4H), 2.9 (d, 2H), 3.0 (s, 3H), 3.7 and 3.8 (s, 2H), 3.9 (m, 3H), 4.5 (m, 1H), 5.1 and 5.3 (m, 2H), 5.8 (m, 1H), 6.9 (m, 4H), 7.1 (m, 4H), 7.4 (d, 2H) and 7.9 (d, 2H).

Starting materials are commercially available, have been described in the literature or can be prepared by adaptation of literature methods. Examples of literature methods include: P. Richter, Ch. Garbe and G. Wagner, *E. Ger. Pharmazie*, **1974**, *29(4)*, 256-262; C. Oniscu, D. Nicoara and G. Funieru, "4-(Ureidosulfonyl)phenylacetic acid and its ureide", *RO79-*

966646, (Romanian document); and M. A. Zahran, M. M. Ali, Y. A. Mohammed and A. A. Shehata, *Int. J. Chem.*, **1993**, *4(3)*, 61.

Method A

4-Methylamino-1-*N*-(3,3-diphenylpropyl)piperidine dihydrochloride

To a solution of 4-tert-butoxycarbonylamino-1-*N*-(3,3-diphenylpropyl)piperidine (Method I) (15.9g, 40mmol) in THF (300ml) was added lithium aluminium hydride (60ml, 1*M* solution in THF, 60mmol) and the mixture was refluxed. After 5h the reaction mixture was cooled and sodium hydroxide was added carefully. The resultant granular precipitate was filtered off and the filtrate partitioned between water and EtOAc. The organic layer was dried ($MgSO_4$) and concentrated to a half of the original volume. 1M HCl in diethyl ether was then added to give the title compound as a white solid (13.8g, 37mmol); MS: 310.

Method B

4-Methylamino-1-*N*-(3-**R**/**S**-phenylbutyl)piperidine dihydrochloride

To a solution of 4-tert-butoxycarbonylamino-1-*N*-(3-**R**/**S**-phenylbutyl)piperidine (Method J) (22 g, 66 mmol) in THF (500ml) was added lithium aluminium hydride (100ml, 1*M* solution in THF, 0.1 mol) and the mixture was refluxed. After 5h the reaction mixture was cooled and 3M sodium hydroxide and water were added carefully. The resultant granular precipitate was filtered off and the filtrate partitioned between water and EtOAc. The organic layer was dried ($MgSO_4$) and concentrated to a half of the original volume. 1M HCl in diethyl ether was then added to give the title compound as a white solid (21 g, 66 mmol); NMR: 1.2 (d, 3H), 2.0 (m, 6H), 2.8 (m, 4H), 3.4 (m, 7H), 7.1 (m, 5H), 9.3 (br s, 1H); MS: 247.

Method C

4-Propargylamino-1-*N*-(3-**R**/**S**-phenylbutyl)piperidine

To a solution of 1-(3-**R**/**S**-phenylbutyl)-4-piperidone (Method K) (500mg, 2.2 mmol) in MeOH (8ml) and acetic acid (2ml) was added propargylamine (0.18ml, 2.6 mmol). After 45mins, sodium cyanoborohydride (170mg, 2.7mmol) was added and the reaction mixture left to stir at ambient temperature. After 16h EtOAc was added and the reaction mixture was partitioned with dilute brine. The organic layer was separated, dried ($MgSO_4$) and concentrated to give the title compound as an oil (330mg, 1.2mmol); MS: 271.

Method D

4-Allylamino-1-*N*-(3,3-diphenylpropyl)piperidine

To a solution of 1-(3,3-diphenylpropyl)-4-piperidone (Method L) (500mg, 2.2 mmol) in MeOH (8ml) and acetic acid (2ml) was added allylamine (0.19ml, 2.6 mmol). After 45mins, sodium cyanoborohydride (135mg, 2.2mmol) was added and the reaction mixture left to stir at ambient temperature. After 16h EtOAc was added and the reaction mixture was partitioned with dilute brine. The organic layer was separated, dried ($MgSO_4$) and concentrated to give the title compound as an oil (170mg, 0.50mmol); MS: 335.

Method E

4-Allylamino-1-*N*-(3-**R**/**S**-phenylbutyl)piperidine

To a solution of 1-(3-**R**/**S**-phenylbutyl)-4-piperidone (Method K) (500mg, 2.2 mmol) in MeOH (8ml) and acetic acid (2ml) was added allylamine (0.19ml, 2.6 mmol). After 45mins, sodium cyanoborohydride (170mg, 2.7mmol) was added and the reaction mixture left to stir at ambient temperature. After 16h EtOAc was added and the reaction mixture was partitioned with dilute brine. The organic layer was separated, dried ($MgSO_4$) and concentrated to give the title compound as an oil (180mg, 0.66mmol); MS: 273.

Method F

4-Piperidinyl-*N*-2-phenylethyl-2,4-difluorophenylurea.trifluoroacetic acid salt

To a solution of 1-tert-butyoxycarbonylpiperidin-4-yl-*N*-2-phenylethyl-2,4-difluorophenylurea (Method O) (300mg, 0.65 mmol) in DCM (4ml) was added trifluoroacetic acid (1ml). After 2h the reaction mixture was concentrated to give the title compound as an oil (0.31g, 0.65mmol); MS: 360.

Method G

4-Amino-1-(3,3-diphenylpropyl)piperidine

To a solution of 4-tert-butoxycarbonylamino-1-*N*-(3,3-diphenylpropyl)piperidine (Method I) (10g, 25 mmol) in DCM (100 ml) was added trifluoroacetic acid (20 ml) dropwise. After 3h, toluene was added and the reaction mixture was concentrated to give the di-trifluoroacetic acid salt of the title compound as an oil (9.7 g, 19 mmol); MS: 295.

Method H

4-Amino-1-(3-**R**/**S**-phenylbutyl)piperidine.ditrifluoroacetic acid salt

To a solution of 4-tert-butoxycarbonylamino-1-(3-**R**/**S**-phenylbutyl)piperidine (Method J) (13.1g, 39.5 mmol) in DCM (150 ml) was added trifluoroacetic acid (30 ml)

dropwise. After 15h, toluene was added and the reaction mixture was concentrated to give the di-trifluoroacetic acid salt of the title compound as an oil (12.8 g, 27.8 mmol); MS: 233.

Method I

4-tert-Butoxycarbonylamino-1-*N*-(3,3-diphenylpropyl)piperidine

To a solution of 4-(Boc-amino) piperidine (10g, 50mmol) in acetonitrile (200ml) was added 3,3-diphenylpropyl bromide (15.1g, 55mmol), tetrabutylammonium iodide (2g, 5mmol) and potassium carbonate (15g, 100mmol) and the mixture refluxed. After 5h the reaction mixture was cooled and poured into water. The solution was partitioned with EtOAc and the organic layer dried ($MgSO_4$), concentrated and purified by column chromatography (toluene: EtOAc, 1:1 with 1% triethylamine) to give the title compound as an oil (15.9g, 40mmol); MS: 395.

Method J

4-*tert*-Butoxycarbonylamino-1-(3-**R/S**-phenylbutyl)piperidine

To a stirred solution of 4-(Boc-amino) piperidine (45g, 0.225mol) in methanol (160ml) was added 3-**R/S**-phenylbutyraldehyde (36.5ml, 0.25mol) followed by acetic acid (15ml). After 1 hour, sodium triacetoxyborohydride (71.5g, 0.34mol) was added portionwise over 30 mins [Caution: effervescence and exotherm]. After 15h water (60 ml) was added and the total mixture was concentrated to remove the methanol. Water (250 ml) was added and the mixture was extracted with EtOAc (3 x 500 ml). The combined organics were washed with water, brine and dried ($MgSO_4$) to give the title compound as a white solid that was further recrystallised from DCM/ EtOAc (54.1 g, 0.163 mol); m pt 220-221°C; NMR: 1.2 (m, 3H), 1.4 (s, 9H), 1.7 (m, 2H), 2.0 (m, 6H), 2.8 (m, 4H), 3.3 (m, 2H), 7.0 (br s, 1H), 7.3 (m, 5H); MS: 333.

Method K

1-(3-**R/S**-phenylbutyl)-4-piperidone

A solution of 1-(3-**R/S**-phenylbutyl)-4-piperidone ethylene ketal (Method M) (6.45 g, 23 mmol) in 6M hydrochloric acid (80ml) was heated to reflux. After 3h the reaction mixture was cooled and the pH was adjusted to pH 10 by the addition of 1M NaOH. The mixture was extracted with DCM (3x30ml) and the combined organics were dried ($MgSO_4$), concentrated and purified by flash column chromatography (DCM to 5% MeOH/DCM) to give the title compound as an oil (2.3 g, 10 mmol); NMR ($CDCl_3$): 1.2 (d, 3H), 1.6 (s, 1H), 1.8 (q, 2H), 2.2-2.5 (m, 5H), 2.7 (m, 3H), 2.8 (q, 1H) and 7.1-7.4 (m, 5H); MS: 232.

Method L

1-(3,3-Diphenylpropyl)-4-piperidone

The procedure described in Method K was repeated using 1-(3,3-diphenylpropyl)-4-piperidone ethylene ketal (Method N) (5.3 g, 16 mmol) in place of 1-(3-**R**/**S**-phenylbutyl)-4-piperidone ethylene ketal to give the title compound as an oil (4.6 g, 16 mmol); NMR ($CDCl_3$): 2.3 (m, 2H), 2.4 (m, 6H), 2.7 (m, 4H), 4.05 (q, 1H) and 7.1-7.4 (m, 10H).

Method M

1-(3-**R**/**S**-Phenylbutyl)-4-piperidone ethylene ketal

To a solution of 4-piperidone ethylene ketal (10g, 70mmol) in MeOH (100ml) was added acetic acid (5ml) and 3-**R**/**S**-phenylbutyraldehyde (11.4 ml, 77mmol) and the reaction mixture left to stir at ambient temperature. After 1h sodium triacetoxyborohydride (21g, 99mmol) was added portionwise. After a further 3h water was added and the methanol was partially removed by evaporation; more water was added and the mixture extracted with EtOAc (x3). The combined organics were washed with water, brine, dried ($MgSO_4$) and concentrated to give the title compound as an oil (17.8g, 65mmol); MS: 276.

Method N

1-(3,3-Diphenylpropyl)-4-piperidone ethylene ketal

To a solution of 4-piperidone ethylene ketal (5g, 35mmol) in acetonitrile (50ml) was added potassium carbonate (9.6g, 70mmol) followed by 3,3-diphenylpropylbromide (9.6g, 35mmol) and tetrabutylammonium hydrogensulphate (1g). After 16h water was added and the acetonitrile was partially removed by evaporation; the mixture was then extracted with EtOAc (x3). The combined organics were washed with water, brine, dried ($MgSO_4$), concentrated and purified by flash column chromatography (DCM to 8% MeOH/DCM) to give the title compound as an oil (5.3g, 16mmol); MS: 338.

Method O

1-tert-Butyoxycarbonylpiperidin-4-yl-*N*-2-phenylethyl-2,4-difluorophenylurea

To a solution of 4-(2-phenylethylamino)-1-tert-butoxycarbonylpiperidine (Method P) (0.61g, 2mmol) in DCM (30ml) was added 2,4-difluorophenylisocyanate (0.21ml, 2mmol). After 3h water was added and the reaction mixture stirred for 20mins. The organic layer was then separated and the aqueous layer partitioned with DCM. The combined organic layers were washed with water, dried ($MgSO_4$), concentrated and columned (20% EtOAc/iso-hexane to 40% EtOAc/iso-hexane) to give the title compound as an oil (0.73g, 1.6mmol); MS:460.

Method P

4-(2-Phenylethylamino)-1-tert-butoxycarbonylpiperidine

To a solution of 1-tert-butoxycarbonylpiperid-4-one (10g, 50mmol) and 2-phenethylamine.hydrochloride (7.9g, 50mmol) in MeOH (250ml) was added sodium cyanoborohydride (6.3g, 100mmol). After 1.5h, water was added carefully and the MeOH was partially removed by evaporation. The mixture was extracted with DCM (x3); the organics were combined and washed with water, dried ($MgSO_4$), concentrated and purified by column chromatography (DCM to 5% MeOH/DCM) to give the title compound as an oil (13.4g, 44mmol); NMR ($CDCl_3$): 1.5 (m, 9H), 1.9 (d, 2H), 2.2 (t, 4H), 2.8 (t, 2H), 2.9 (m, 2H), 3.0 (m, 2H), 3.85 (m, 1H), 4.1 (m, 2H) and 7.2-7.4 (m, 5H).

Method R

4-(Cyclopropylmethyl)amino-1-(3-**R/S**-phenylbutyl)piperidine

To a solution of 1-(3-**R/S**-phenylbutyl)-4-piperidone (Method K) (500mg, 2.2 mmol) in MeOH (8ml) and acetic acid (2ml) was added cyclopropylmethylamine (0.2ml, 2.6 mmol). After 45mins, sodium cyanoborohydride (170mg, 2.7mmol) was added and the reaction mixture left to stir at ambient temperature. After 16h EtOAc was added and the reaction mixture was partitioned with dilute brine. The organic layer was separated, dried ($MgSO_4$) and concentrated to give the title compound as an oil (230mg, 1.2mmol); MS: 287.

Method S

4-Fluorocinnamanic acid tert-butyl ester

To a suspension of 4-fluorocinnamanic acid (1.66g, 10mmol) in toluene (15mL) heated to 80°C, was added dimethylformamide di-tert-butylacetal (8.2g, 40 mmol) dropwise, and the reaction heated for a further 30 minutes. Upon cooling, the reaction was partitioned between toluene and water (15mL), and washed with $NaHCO_3$ solution (2x10mL), and brine (10mL). The organic layer was dried, and concentrated. Purified on a Bond Elut column (eluent DCM) to afford the desired product as a colourless oil (1.25 g, 5.6mmol); NMR ($CDCl_3$): 1.57 (9H, s), 6.28 (1h, d), 7.07 (2H, t) and 7.50 (3H, m).

Method T

3-Phenyl-3-(4-fluorophenyl)propionic acid tert-butyl ester

To a -78°C solution of 4-fluorocinnamanic acid tert-butyl ester (Method S) (0.9g, 4mmol) in THF was added dropwise a solution of phenyllithium in hexanes (4 mL of 1.5M solution, 6 mmol). The reaction was stirred for 1h and then quenched with water and extracted

into EtOAc, dried and purified by Bond Elut chromatography (50:50 DCM/iso-hexane) to afford the title compound, as a colourless oil (500 mg, 1.8mmol); NMR ($CDCl_3$): 1.21 (9H, s), 2.87 (2H, d), 4.40 (1H, t), 6.90 (2H, t) and 7.15 (7H, m).

Method U

3-Phenyl-3-(4-fluorophenyl)-propan-1-ol

To a THF (10 mL) solution of 3-phenyl-3-(4-fluorophenyl)-propionic acid, tert-butyl ester (Method T) (495mg, 1.65mmol) was added $LiAlH_4$ in THF (2.5 mL of a 1.0M solution) and the reaction stirred at RT for 2h. The reaction mixture was quenched cautiously with 2M aqueous NaOH, and the precipitate removed. The solution was then extracted with EtOAc, washed with water (20 mL) dried, $MgSO_4$, and evaporated to afford the title compound as a pale solid, (379 mg, 1.65mmol); NMR ($CDCl_3$): 2.23 (2H, m), 3.65 (2H, t), 4.06 (1H, t), 6.90 (2H, m) and 7.20 (7H, m).

Method V

3-Phenyl-3-(4-fluorophenyl)-1-bromopropane

To a solution of 3-phenyl-3-(4-fluorophenyl)-propan-1-ol (Method U) (379mg, 1.65mmol) in DCM (5 mL), was added carbon tetrabromide (564 mg, 1.7 mmol), and triphenyl phosphine (445 mg, 1.7 mmol). The reaction was stirred overnight, and filtered through a pad of silica, then evaporated. The title product was obtained as a pale white solid by Bond Elut chromatography, eluent iso-hexane, (415 mg, 86%); NMR ($CDCl_3$): 2.43 (2H, m), 3.20 (2H, t), 4.16 (1H, t), 6.90 (2H, m) and 7.20 (7H, m).

Method W

4,4-Di-(4-fluorophenyl)-1-iodobutane

To a suspension of sodium iodide (1.5 g, 10 mmol) in acetone (100 mL) was added 4,4-di(4-fluorophenyl)-1-chlorobutane (2 g, 7 mmol), and refluxed for 5h. The acetone was evaporated and the product was partitioned between water and EtOAc. The organic phase was dried ($MgSO_4$) and evaporated to give the title compound as a pale yellow oil, (3 g, 2:1 mixture of product to starting material); NMR ($CDCl_3$): 1.80 (2H, m), 2.20 (2H, m), 3.20 (1 1/3H, t, CH_2I), 3.55 (2/3H, t, CH_2Cl), 3.90 (1H, t), 6.96 (4H, m) and 7.16 (4H, m).

Method X

4,4-Di-(4-fluorophenyl)-but-1-ene

The crude 4,4-di-(4-fluorophenyl)iodobutane (Method W) (3 g) was added to potassium *tert*-butoxide (1.3 g, 12 mmol) in THF (30 mL), and stirred overnight. The product

was extracted into EtOAc and washed with water (100 mL). The organic phase was dried ($MgSO_4$) and evaporated to afford a yellow oil. This was purified by chromatography (silica, *iso*-hexane) to afford the desired product as a colourless oil. (1.4 g, 82%); NMR: 2.80 (2H, t), 4.00 (1H, t), 4.98 (1H, dd) 5.05 (1H, dd), 5.70 (1H, ddt), 7.00 (4H, m) and 7.20 (4H, m).

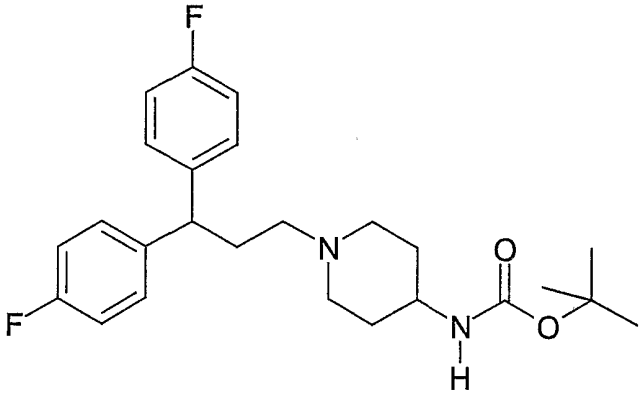
Method Y

3,3-Di-(4-fluorophenyl)propanal

A DCM solution of 4,4-di-(4-fluorophenyl)-but-1-ene (Method X) (1.4 g, 5.7 mmol, in 20 mL) was cooled to -78°C and exposed to ozone until a pale blue colour persisted (about 20 min). The reaction was then purged with oxygen until the colour faded, and finally quenched with triphenylphosphine (1.49 g, 5.7 mmol). Upon warming to RT the reaction was washed with water, dried ($MgSO_4$) and concentrated. The residue was passed through a plug of silica to afford the title product as a colourless oil, (1.18 g, 100%); NMR ($CDCl_3$): 3.15 (2H, d), 4.60 (1H, t), 7.00 (4H, m), 7.18 (4H, m), 9.75 (1H, s).

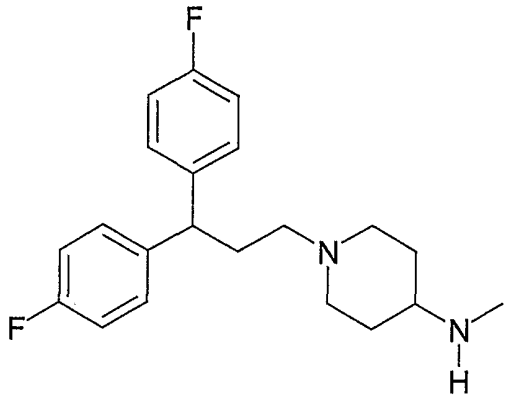
Method Z

1-(3,3-Di-[4-fluorophenyl]propyl)-4-([tert-butoxycarbonyl]amino)piperidine



To a solution of 3,3-di-(4-fluorophenyl)propanal (Method Y) (1.18 g, 5.7 mmol), in dichloroethane (14 mL) and 4-Bocaminopiperidine (1.2 g, 6 mmol) was added acetic acid (0.3 mL), 3Å molecular sieves (2 g), and sodium triacetoxyborohydride (1.27 g, 6 mmol), and the reaction mixture stirred for 5h. The mixture was poured onto water and extracted into EtOAc (30 mL), dried and evaporated. The title product was obtained by purification by chromatography (silica, 5% MeOH/DCM) to give the product as a solid (1.7 g, 69%); MS: 431.

Method AA

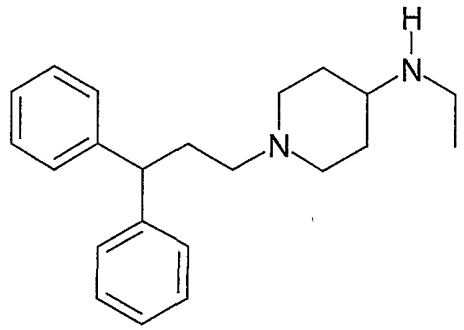


1-(3,3-Di-[4-fluorophenyl]propyl)-4-(methylamino)piperidine

To a solution of 1-(3,3-Di-[4-fluorophenyl]propyl)-4-([*tert*-butoxycarbonyl]amino)piperidine (Method Z) (1.7 g, 3.9 mmol) in THF (50 mL), was added $LiAlH_4$ solution (5 mL of a 1.0M solution in THF) dropwise (CARE gas evolution) and then the reaction was refluxed for 16h. The reaction mixture was then cooled to RT and cautiously quenched with 2M NaOH, filtered to remove precipitate and partitioned between water and EtOAc. The organic layer was dried over $MgSO_4$ and evaporated. The crude product was purified by chromatography (silica, eluent 1:1, toluene:EtOAc with 0.5% isopropylamine) to afford the title compound as a yellow oil (500 mg, 37%); NMR: 2.2-1.0 (9H, m), 2.67 (1H, m), 3.4-3.2 (4H, m), 3.90-4.10 (2H, m), 4.35 (2H, m), 7.05 (4H, m) and 7.30 (4H, m); MS: 345.

Method AB

4-Ethylamino-1-*N*-(3,3-diphenylpropyl)piperidine

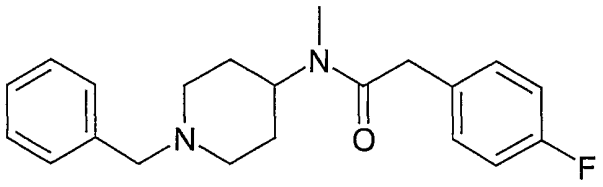


To a solution of 1-(3,3-diphenylpropyl)-4-piperidone (Method L) (2.2g, 7.5mmol) in DCM (30ml) was added ethylamine (8.5ml, 2M in THF, 17mmol), sodium triacetoxyborohydride (1.6g, 7.5mmol) and 4Å Molecular Sieves (10 rods). The reaction mixture left to stir at ambient temperature. After 16h the mixture was filtered, washed with

water, dried (Na_2SO_4) and concentrated to give the title compound as an oil (1.4g, 4.35mmol); MS: 323.

Method AC

N-[1-Phenylmethyl-piperidin-4-yl]-*N*-methyl-(4-fluorophenyl)acetamide

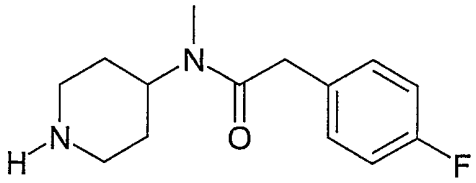


To a solution of 4-methylamino-1-*N*-(phenylmethyl)piperidine† (2.95g, 14.5mmol) in DMF (25ml) was added DIPEA (10ml), 4-fluorophenylacetic acid (2.67g, 17.3mmol) and HATU (6.0g, 16mmol). After 16h at RT water was added and the mixture was partitioned with EtOAc (x3). The organics were combined, washed with water and brine, dried ($MgSO_4$) and concentrated to give the title compound as a brown oil (4.90g, 14.4mmol); MS: 341.

† 4-Methylamino-1-*N*-(phenylmethyl)piperidine is described in *J. Med. Chem.* **1999**, *42*, 4981-5001.

Method AD

4-(*N*-(4-Fluorophenylacetamido)-*N*-methyl)aminopiperidine



To a solution of *N*-[1-phenylmethyl-piperidin-4-yl]-*N*-methyl-(4-fluorophenyl)acetamide (Method AC) (4.90g, 14.4mmol) in EtOH (50ml) was added 20% palladium hydroxide on carbon (1g) followed by ammonium formate (5.18g, 82mmol). The reaction mixture was then refluxed until the evolution of gas ceased at which point it was filtered through Celite® and concentrated to give the title compound as an oil (2.86g, 11.4mmol); MS: 251.

Method AE

3-Phenylpent-4-enoic acid

Cinnamyl alcohol (5g, 37mmol), triethylorthoacetate (47ml) and propionic acid (0.17ml) were heated at 140°C under a distillation head and condenser. After 1h the reaction mixture was cooled and concentrated to give a pale yellow oil. This oil was dissolved in

EtOH (15ml) and water (15ml) and NaOH (3.73g, 93mmol) was added and the mixture stirred at 80°C. After 16h the mixture was heated to 100°C for 2h then allowed to cool. The reaction mixture was diluted with water (120ml) and extracted with diethyl ether (2x150ml). The aqueous layer was acidified with AcOH and then re-extracted with diethyl ether (3x150ml). The organics were combined and dried ($MgSO_4$) and concentrated to give the desired product as a brown oil (5.52g, 31mmol); NMR: 2.65 (m, 2H), 3.75 (1, 1H), 4.95 (s, 1H), 5.05 (d, 1H), 5.95 (m, 1H), 7.2 (m, 5H), 12.1 (br s, 1H); MS: 177.

Method AF

3-Phenylpent-4-en-1-ol

To a solution of 3-phenylpent-4-enoic acid (Method AE) (2.0g, 11.4mmol) in THF (20ml) at 0°C was added lithium aluminium hydride (12.5ml, 1M solution in THF) dropwise over 15 mins and the reaction mixture was allowed to warm to RT. After 64h water (2.4ml) was added followed by 2N NaOH (2.4ml) then water (7.2ml). The resulting gelatinous precipitate was filtered, washed with THF and concentrated. The residue was dissolved in DCM and washed with saturated sodium hydrogen carbonate (2x150ml), dried ($MgSO_4$) and concentrated to give the title compound as a pale yellow oil (1.8g, 11.1mmol); NMR: 1.8 (m, 2H), 3.4 (m, 2H), 4.4 (t, 1H), 5.0 (m, 2H), 5.9 (m, 1H) and 7.2 (m, 5H).

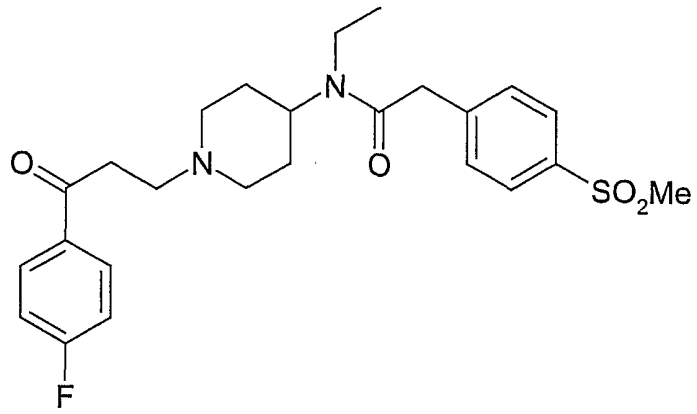
Method AG

5-Bromo-3-phenylpent-1-ene

The procedure described in Method V was repeated except using 3-phenylpent-4-en-1-ol (1.75g, 10.8mmol), triphenylphosphine (3.12g, 11.9mmol), carbon tetrabromide (3.94g, 11.9mmol) and DCM (35ml) to give the title compound as a colourless oil (2.02g, 9mmol); NMR: 2.2 (m, 2H), 3.4 (m, 3H), 5.1 (m, 2H), 5.95 (m, 1H) and 7.2 (m, 5H).

Method AH

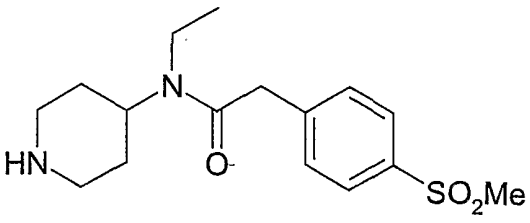
N-[1-(3-[4-Fluorophenyl]-3-oxopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide hydrochloride



To a solution of *N*-4-piperidinyl-*N*-ethyl-4-methanesulfonylphenylacetamide (1.3 g, 4.0 mmol) in DMF (25 mL) was added DIPEA (2 mL, 11.5 mmol) and 3-chloro-4'-fluoropropiophenone (770 mg, 4.0 mmol). The resulting mixture was stirred at room temperature overnight then evaporated. The residue was heated to reflux with 5% methanol in ethyl acetate giving a white solid which was isolated (1.6 g, 80%). NMR: 1.00 and 1.16 (t, 3H), 1.75 (t, 2H), 2.23 (q, 2H), 3.10 (t, 2H), 3.18 (s, 3H), 3.30 (m, 2H), 3.35 and 3.64 (q, 2H), 3.56 (m, 2H), 3.82 and 3.93 (s, 2H), 4.15 and 4.28 (m, 1H), 7.40 (m, 2H), 7.50 (m, 2H), 7.83 (m, 2H), 8.07 (m, 2H); MS: 475.

Method AI

N-(4-Piperidinyl)-*N*-ethyl-4-methanesulfonylphenylacetamide

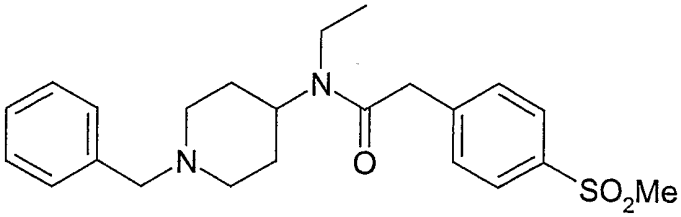


To a solution of *N*-(1-phenylmethyl-4-piperidinyl)-*N*-ethyl-4-methanesulfonylphenyl-acetamide (34g, 82mmol) in ethanol (600mL) was added ammonium formate (40g). The mixture was purged with argon and 30% Pd on carbon (4.2g) was added. The resulting mixture was stirred at reflux for 4 h, then allowed to cool and filtered through diatomaceous earth. The filtrate was evaporated to give a thick oil which solidified on standing to yield the title compound (24.9 g, 94%); NMR: 1.02 and 1.15 (t, 3H), 1.4 -1.6 (br m, 4H), 2.45 (m, 2H),

2.93 (br m, 2H), 3.18 (s, 3H), 3.20 and 3.32 (q, 2H), 3.72 and 4.18 (m, 1H), 3.80 and 3.87 (s, 2H), 7.50 (m, 2H), 7.85 (m, 2H); MS: 325 (MH+).

Method AJ

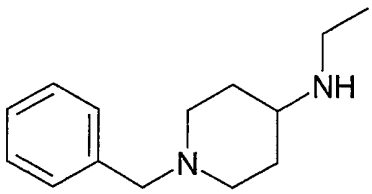
N-(1-Phenylmethyl-4-piperidinyl)-*N*-ethyl-4-methanesulfonylphenylacetamide



To a solution of 1-phenylmethyl-4-ethylaminopiperidine dihydrochloride (32.0g, 110mmol) in DCM (500mL) was added N,N-diisopropylethylamine (60mL) with stirring to ensure complete dissolution. 4-Methanesulfonylphenylacetic acid (25.0g, 117mmol), 4-Dimethylaminopyridine (4-DMAP) (2.0g) and dicyclohexylcarbodiimide (DCCI) (25.0g, 121 mmol) were added and the resulting mixture was stirred at room temperature for 20 h. The precipitate was removed by filtration and the resulting solution was washed successively with 2N aqueous HCl, water and 1N aqueous NaOH, dried ($MgSO_4$) and evaporated. The residue was purified by silica gel chromatography (eluent 10% MeOH/ethyl acetate) to afford the title compound (35 g, 76%); NMR: 1.00 and 1.14 (t, 3H), 1.45 and 1.70 (m, 2H), 1.95 (br m, 2H), 2.80 (br m, 2H), 3.18 (s, 3H), 3.20 and 3.33 (q, 2H), 3.45 (s, 2H), 3.80 and 3.87 (s, 2H), 3.70 and 4.10 (m, 1H), 7.2 - 7.3 (m, 5H), 7.48 (m, 2H), 7.82 (m, 2H); MS: 415 (MH+).

Method AK

1-Phenylmethyl-4-ethylaminopiperidine dihydrochloride

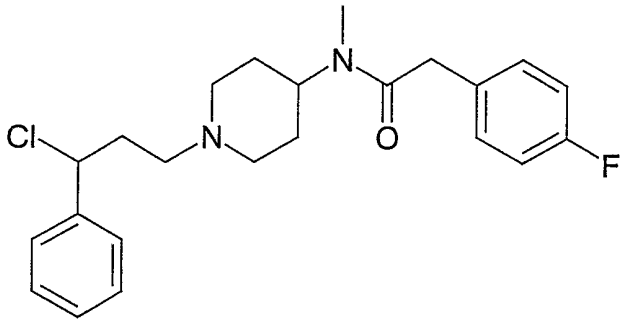


To a solution of 1-phenylmethyl-4-piperidone (25.0 g, 132 mmol) in THF (250 mL) was added ethylamine hydrochloride (12.0 g, 147 mmol) and methanol (50 mL) and the resulting mixture stirred at room temperature for 10 min. Sodium triacetoxyborohydride (40 g, 189 mmol) was added portionwise and the resulting mixture stirred at room temperature for 1 h. 2M Sodium hydroxide solution (250 mL) was added and the resulting mixture extracted with diethyl ether. The organic extracts were dried (K_2CO_3) and evaporated to give 1-phenylmethyl-4-ethylaminopiperidine as an oil. This was dissolved in ethanol (500 mL) and

concentrated hydrochloric acid (20 mL) was added. The resulting crystals were collected, washed with diethyl ether and dried giving the title compound as a solid (38 g); NMR: ($CDCl_3$): 1.10 (t, 3H), 1.40 (m, 2H), 1.83 (m, 2H), 2.02 (m, 2H), 2.65 (q, 2H), 2.85 (m, 2H), 3.50 (s, 2H), 3.75 (m, 1H), 7.2 - 7.4 (m, 5H); MS: 219 (MH+).

Method AL

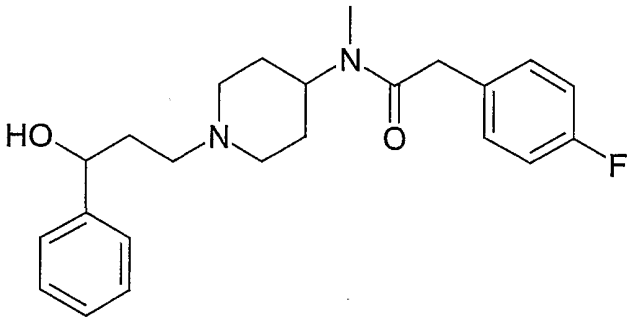
N-[1-(3-Phenyl-3-chloropropyl)-4-piperidinyl]-*N*-methyl-4-fluorophenylacetamide



To a cooled (5°C) solution of *N*-[1-(3-phenyl-3-hydroxypropyl)-4-piperidinyl]-*N*-methyl-4-fluorophenylacetamide (112 mg, 0.29 mmol) in DCM (5 mL) was added N,N-diisopropylethylamine (0.10 mL, 0.58 mmol) then methanesulfonyl chloride (0.03 mL, 0.35 mmol). The resulting mixture was stirred at ambient temperature for 18 h, then was concentrated. The residue was purified by Bond Elut chromatography (eluent DCM, followed by 5% MeOH/DCM) to afford the title compound as an oil (120mg) which was characterised by LC-MS; MS: 403, 405.

Method AM

N-[1-(3-Phenyl-3-hydroxypropyl)-4-piperidinyl]-*N*-methyl-4-fluorophenylacetamide

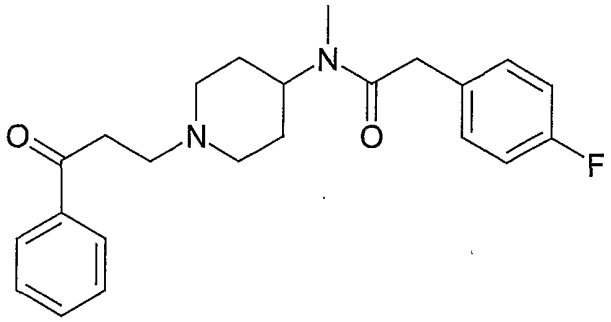


To a solution of *N*-[1-(3-phenyl-3-oxopropyl)-4-piperidinyl]-*N*-methyl-4-fluorophenylacetamide (300 mg, 0.78 mmol) in methanol (30 mL) was added sodium borohydride (120 mg) and the resulting mixture was stirred at room temperature for 2 h. Water (5 mL) was added and the mixture was concentrated. The residue was extracted with

DCM and the organic extract was washed with water and brine, dried and concentrated to give the title compound (230 mg, 76%); NMR: 1.4 (m, 2H), 1.7 (m, 4H), 1.9 (m, 2H), 2.7 and 2.8 (s, 3H), 2.9 (m, 2H), 3.65 and 3.75 (s, 2H), 4.2 (m, 1H), 4.6 (m, 1H), 5.4 (br s, 1H), 7.1 (m, 2H), 7.2 (m, 3H), 7.3 (m, 4H); MS: 385.

Method AN

N-[1-(3-Phenyl-3-oxopropyl)-4-piperidinyl]-*N*-methyl-4-fluorophenylacetamide



To a solution of *N*-(4-piperidinyl)-*N*-methyl-4-fluorophenylacetamide (250 mg, 1.0 mmol) in DMF (10 mL) was added 3-chloropropiophenone (168 mg, 1.0 mmol) and DIPEA (0.35 mL, 2.0 mmol). The resulting mixture was stirred at room temperature for 3 h. Water and DCM were added and the phases separated. The organic phase was washed with brine, dried and concentrated. The residue was purified by silica column chromatography (eluent 10% MeOH in DCM) yielding the title compound (305 mg); NMR: 1.3 (m, 2H), 1.6 (m, 2H), 2.0 (m, 2H), 2.6 (s, 3H), 2.7 (m, 2H), 2.9 (m, 2H), 3.1 (t, 2H), 3.7 (m, 2H), 4.2 (m, 1H), 7.1 (m, 2H), 7.2 (m, 2H), 7.4 (dd, 2H), 7.6 (t, 1H), 7.9 (d, 2H); MS: 383.

Method AO

N-(2-Bromoethyl)diphenylamine

To a cooled (5°C) solution of *N,N*-diphenylbromoacetamide (1.4 g, 5.0 mmol) in THF (20 mL) was added borane methyl sulfide complex (26 mL, 1.0M) gradually. The reaction mixture was stirred at room temperature for 4 h. 10% Acetic acid in methanol (30 mL) was added and the resulting mixture was stirred for 20 h. The solvent was removed by evaporation and the residue was partitioned between ethyl acetate and water. The organic phase was dried and concentrated to give the title compound (1.0 g); NMR (CDCl3): 3.52 (t, 2H), 4.10 (t, 2H), 7.00 (m, 4H), 7.23 (m, 6H).

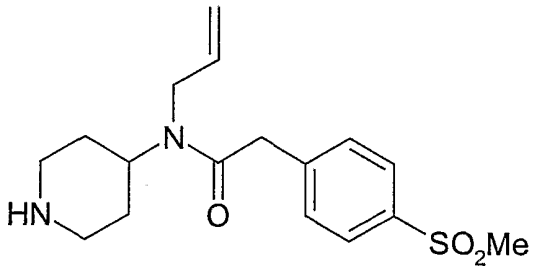
Method AP

N,N-Diphenylbromoacetamide

To a cooled (5°C) solution of diphenylamine (2.0 g, 12 mmol) in DMF (15 mL) was added sodium hydride (520 mg, 60% dispersion) followed by bromoacetyl bromide (3.58 g) and the resulting mixture was stirred for 2 h. Water was added gradually, then the mixture was extracted three times with ethyl acetate. The combined organic extracts were washed three times with brine, dried ($MgSO_4$) and evaporated to yield the title compound (3.4 g, 99%); NMR ($CDCl_3$): 3.83 (S, 2H), 7.35 (m, 10H).

Method AQ

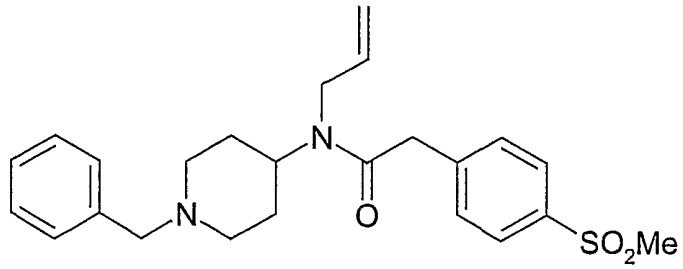
N-(4-Piperidinyl)-*N*-allyl-4-methanesulfonylphenylacetamide



To a solution of *N*-(1-phenylmethyl-4-piperidinyl)-*N*-allyl-4-methanesulfonylphenylacetamide (4.40 g, 10.3 mmol) in DCM (30 mL) under an argon atmosphere and the mixture cooled in an ice-water bath. 1-Chloroethyl chloroformate (1.34 mL, 12.4 mmol) was added and the resulting mixture was stirred for 3 h while warming to room temperature. The mixture was evaporated and the residue dissolved in methanol (30 mL). The resulting mixture was refluxed for 1 h, allowed to cool and concentrated. The crude product was purified by silica column chromatography (eluent 5%EtOH/DCM then 15%EtOH/2% isopropylamine/DCM) to give the title compound (1.30 g); NMR: 1.50 (m, 4H), 2.50 (m, 2H), 2.95 (m, 2H), 3.20 (s, 3H), 3.74 and 3.91 (s, 1H), 3.80 and 3.95 (d, 1H), 4.29 (m, 1H), 5.00 and 5.05 (d, 1H), 5.20 (m, 1H), 5.73 and 5.89 (dddd, 1H), 7.44 and 7.49 (d, 2H), 7.85 (m, 2H).

Method AR

N-(1-Phenylmethyl-4-piperidinyl)-*N*-allyl-4-methanesulfonylphenylacetamide



This was prepared by reacting 1-phenylmethyl-4-allylamine with 4-methanesulfonylphenylacetamide according to the procedure used for Method AJ; NMR (d6-DMSO, 373K): 1.65 (m, 2H), 1.88 (m, 2H), 2.39 (m, 2H), 3.05 (m, 2H), 3.09 (s, 3H), 3.75 (m, 4H), 3.93 (s, 2H), 4.08 (m, 1H), 5.15 (m, 2H), 5.82 (dddd, 1H), 7.30 (m, 5H), 7.45 (d, 2H), 7.80 (d, 2H).

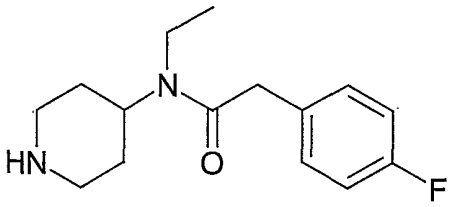
Method AS

1-Phenylmethyl-4-allylamine

This was prepared by reacting 1-phenylmethyl-4-piperidone with allylamine according to the procedure used for Method AK; NMR ($CDCl_3$): 1.4 (m, 2H), 1.5 (m, 2H), 1.9 (m, 2H), 2.0 (dd, 2H), 2.5 (m, 1H), 2.8 (m, 2H), 3.3 (d, 2H), 3.5 (s, 3H), 5.1 (d, 1H), 5.2 (d, 1H), 5.9 (dddd, 1H), 7.3 (m, 5H); MS: 231 (MH+).

Method AT

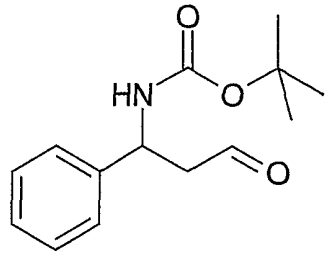
N-4-Piperidinyl-*N*-ethyl-4-fluorophenylacetamide



This was prepared by reacting *N*-(1-phenylmethyl-4-piperidinyl)-*N*-ethyl-4-fluorophenylacetamide according to the procedure used for Method AI; NMR: (formic acid salt): 0.97 and 1.10 (t, 3H), 1.46 and 1.62 (m, 2H), 1.8 - 2.0 (m, 2H), 2.78 (m, 2H), 3.1 - 3.3 (m, 4H), 3.65 and 3.74 (s, 2H), 3.97 and 4.22 (m, 1H), 7.08 (m, 2H), 7.25 (m, 2H), 8.42 (s, 1H); MS: 265.

Method AU

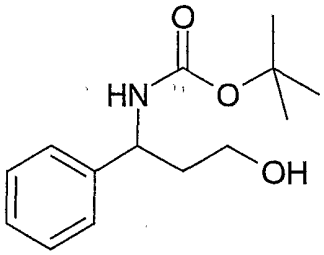
3-Phenyl-3-Boc-aminopropanal



A solution of 3-phenyl-2-Boc-aminopropanol (700 mg, 2.78 mmol) in DCM (8 mL) was added to a stirred solution of Dess-Martin periodinane (1.30 g, 3.06 mmol) in DCM (5 mL) at room temperature followed by pyridine (0.3 mL). After stirring for 6 h at room temperature the mixture was partitioned between diethyl ether and saturated aqueous sodium bicarbonate solution containing sodium thiosulfate. The organic phase was washed with water and brine, dried and concentrated giving the title compound as a solid (790 mg); NMR: 1.4 (s, 9H), 2.8 (m, 2H), 5.1 (m, 1H), 7.3 (m, 5H), 8.6 (m, 1H), 9.6 (t, 1H).

Method AV

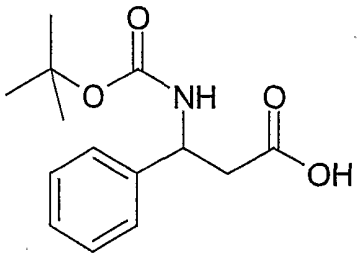
3-Phenyl-2-Boc-aminopropanol



To a solution of 3-phenyl-3-Bocaminopropanoic acid (1.0 g, 3.78 mmol) in THF (10 mL) was added borane-THF complex (7.5 mL, 1.5M, 11.3 mmol) at 0°C. The resulting mixture was stirred with warming to room temperature for 5 h. 10% Acetic acid in methanol (20 mL) was added dropwise, the resulting mixture was concentrated and the residue partitioned between DCM and 1M aqueous HCl. The organic phase was washed with water and brine, dried ($MgSO_4$) and concentrated. The residue was purified by Bond Elut chromatography (eluent 5% MeOH/DCM) to afford the title compound (900 mg).

Method AW

3-Phenyl-3-Boc-aminopropanoic acid



To a solution of DL-3-amino-3-phenylpropanoic acid (5 g, 30.2 mmol) in 2M aqueous sodium hydroxide (70 mL) was added a solution of di-tert-butyldicarbonate (8.56 g, 39.2 mmol) in THF (60 mL) and the resulting mixture stirred at room temperature for 48 h. Water (50 mL) was added and the mixture washed twice with ethyl acetate (50 mL). The aqueous phase was acidified to pH 3 with concentrated aqueous HCl, and the resulting mixture was extracted twice with ethyl acetate (60 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to give the title compound as a white solid (4.8 g); NMR: 1.4 (s, 9H), 2.7 (m, 2H), 4.8 (m, 1H), 7.3 (m, 5H), 7.5 (br d, 1H), 12.1 (br s, 1H); MS: 266.

Method AX

4-Cyclopropylamino-1-(3,3-diphenylpropyl)piperidine

This was prepared using a method similar to that used for 4-ethylamino-1-(3,3-diphenylpropyl)piperidine (Method AB). NMR: 0.0 (m, 2H), 0.2 (m, 2H), 1.1 (m, 2H), 1.55 (m, 2H), 1.7 (m, 2H), 1.9 (m, 5H), 2.5 (m, 2H), 3.7 (m, 1H), 6.9 (m, 2H), 7.1 (m, 8H); MS: 335.

Method AY

4-(2-Hydroxyethylamino)-1-(3,3-diphenylpropyl)piperidine

This was prepared using a method similar to that used for 4-ethylamino-1-(3,3-diphenylpropyl)piperidine. NMR: 1.2 (m, 2H), 1.7 (m, 2H), 1.9 (t, 2H), 2.1 (m, 4H), 2.3 (m, 1H), 2.7 (m, 2H), 3.1 (s, 3H), 3.4 (m, 1H), 3.95 (m, 1H), 7.1 (m, 2H), 7.3 (m, 8H); MS: 339.

Method AZ

4-(2-Fluoroethylamino)-1-(3,3-diphenylpropyl)piperidine

This was prepared using a method similar to that used for 4-ethylamino-1-(3,3-diphenylpropyl)piperidine; MS: 341.

Method BA

4-Chlorosulfonylphenylacetic acid.

Chlorosulfonic acid (10ml, 148 mmol) was heated to 40°C and phenyl acetic acid (5g, 36.7 mmol) was added slowly. Stirred for two hours then cooled and carefully poured onto ice (50g). The filtrate was cooled by filtration and dried under vacuum to afford the title compound as a pale cream solid. (7.9g, 92%); NMR ($CDCl_3$), 3.80 (2H, s), 7.68 (2H, d), 8.00 (2H, d); MS: ES- 233, ES+ 189.

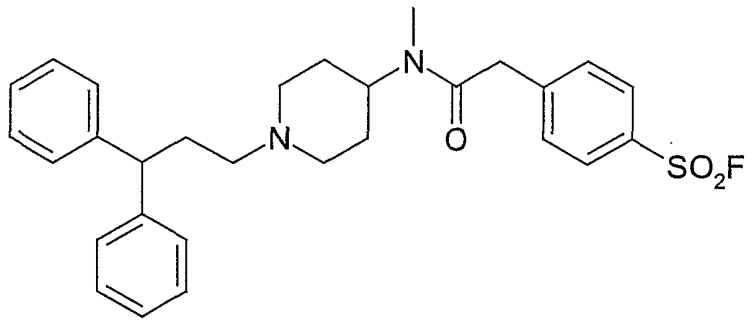
Method BB

4-Fluorosulfonylphenylacetic acid.

18-Crown-6 (63mg, 1mol%) was added to a solution of 4-chlorosulfonylphenylacetic acid (5g, 24 mmol) and KF (2.78g, 48 mmol) in MeCN (5mL) and stirred for 4 h. The product was then drowned out by the addition of water (100mL) and collected by filtration to afford desired product (4.78g, 97%); NMR ($CDCl_3$): 3.80 (2H, s), 7.68 (2H, d), 8.00 (2H, d); MS: 187.

Method BC

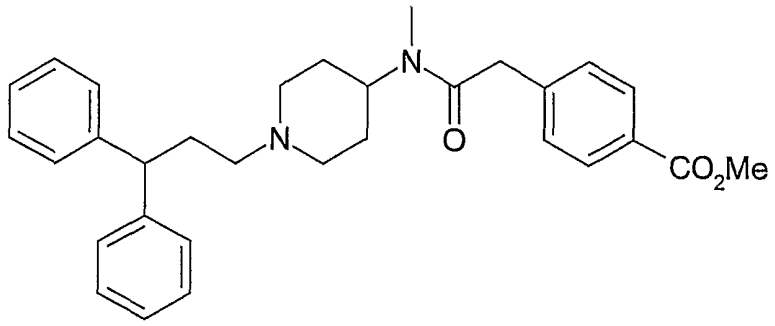
N-[1-(3,3-Diphenylpropyl)-4-piperidinyl]-*N*-methyl-4-fluorosulfonylphenylacetamide



To a solution of HATU (836mg, 2.2mmol), 4-fluorosulfonylphenylacetic acid (409mg, 2.2 mmol), 1-(3,3-diphenylpropyl)-4-methylaminopiperidine (618mg, 2 mmol) in DMF (10 mL) was added DIPEA (0.4mL) and stirred over night. Poured onto water and extracted into ethyl acetate (50 mL). Washed (brine 100mL) and dried over $MgSO_4$, and evaporated to afford a pale yellow solid. Trituration with ethyl acetate/hexane (50:50) afforded the title product as a pale yellow solid (577 mg, 57%); NMR: 1.80 (2H, m), 2.00 (2H, m), 2.40 (2H, m), 2.80-3.20 (6H, m), 3.27 (3H, s), 3.45 (2H, m), 3.92 (1H, m), 4.46 (1H, m), 7.20 (2H, m), 7.27 (8H, m), 7.60 (2H, t), 8.04 (2H, d); MS: 509.

Method BD

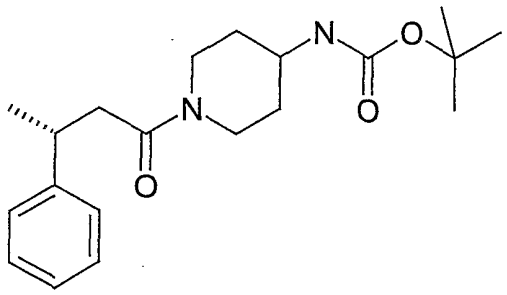
N-[1-(3,3-diphenylpropyl)-4-piperidinyl]-*N*-methyl-4-methoxycarbonylphenylacetamide



Solid HATU (2.55 g; 6.7 mmol) followed by DIPEA (1.22 ml; 6.7 mmol) was added at room temperature to a solution of 4-methoxycarbonylphenylacetic acid (1.3 g; 6.7 mmol) in DMF (10 ml). After 5 minutes, 4-methylamino-1-(3,3-diphenylpropyl)piperidine (2.1 g; 6.7 mmol) was added and stirring continued overnight at ambient temp. The mixture was then partitioned between water (10 ml) and ethyl acetate (10 ml). The organic layer was separated, washed with water (1 ml) and dried over Na_2SO_4 and evaporated to give an oil. Purification was by Bond Elut, eluting with a stepped gradient from DCM to 5% methanol in DCM yielding the title compound (2.47 g, 77%); MS: 485 (MH^+).

Method BE

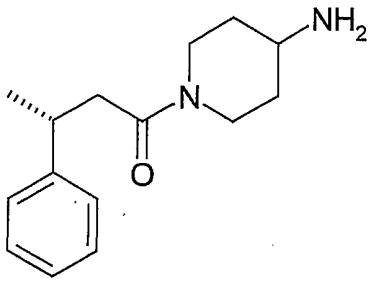
4-*tert*-Butoxycarbonylamino-1-(3-**R**-phenyl-1-butanoic amide)piperidine



To a solution of 4-Boc-amino piperidine (2.46g, 12.3 mmol) in DMF (30 mL) was added HATU (4.67g, 12.3 mmol) and 3-**R**-phenyl-1-butanoic acid(2g, 12.2 mmol) and DIPEA (2.12 mL). Stirred over night then poured into water and extracted into ethyl acetate. The organic extracts were dried over $MgSO_4$ and evaporated to afford the title compound as a white solid, (4.03 g, 94%); NMR: 1.20 (6H, m), 1.38 (9H, s), 1.65 (2H, m), 2.60 (2H, m), 3.00 (1H, m), 3.15 (1H, q), 3.40 (1H, m), 3.80 (1H, d, broad), 4.20 (1H, m), 6.80 (1H, m), 7.18 (1H, m), 7.24 (4H, m) MS: 347, 291 (– BOC).

Method BF

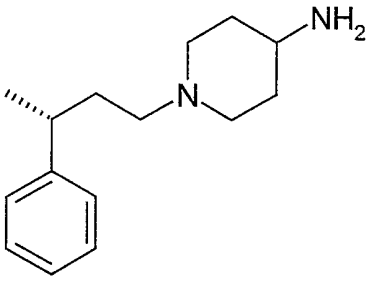
4-Amino-1-(3-**R**-phenyl-1-butanoic amide)piperidine hydrochloride



To a solution of acetyl chloride (5mL) in methanol (20mL) was 4-Boc-amino-1-(3-**R**-phenyl-1-butanoic amide)piperidine (1g, 3mmol) and stirred for one hour. The solvents were then evaporated to afford the title compound as a white solid. (929mg, 100% for HCl salt); NMR: 1.20 (3H, d), 1.35 (2H, m), 1. 41 (1H, m), 1.89 (2H, m), 2.80-3.20 (5H, m), 3.90 (1H, d), 4.30 (1H, d), 7.10 (1H, m), 7.20 (4H, m); MS: 247.

Method BG

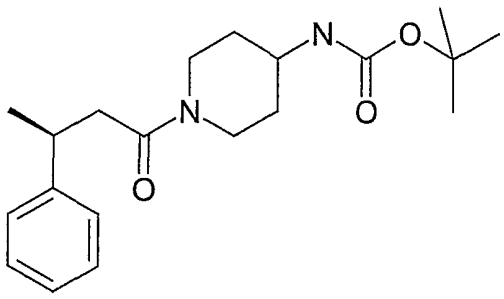
4-Amino-1-(3-**R**-phenylbutyl)piperidine



To a solution of 4-amino-1-(3-**R**-phenyl-1-butanoic amide)piperidine(1g, 3 mmol) in THF (20mL) was added a solution of $LiAlH_4$ in THF (10 mL of 1.0M solution) and the mixture was refluxed for 5 hours. The mixture was cooled, quenched with aqueous sodium hydroxide, filtered and the filtrate partitioned between water and ethyl acetate. The combined organic phase was dried, $MgSO_4$, and evaporated to afford the title compound as a white solid. (610 mg, 87 %); NMR: 1.20 (4H, m), 1.60 (4H, m), 1.89 (2H, m), 2.10 (2H, m), 2.43 (1H, m), 2.70 (4H, m), 7.10 (3H, m), 7.20 (2H, m); MS: 233.

Method BH

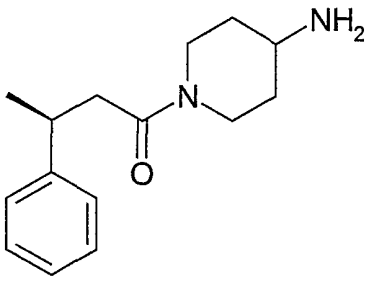
4-*tert*-Butoxycarbonylamino-1-(3-S-phenyl-1-butanoic amide)piperidine



To a solution of 4-Boc-amino piperidine (2.46g, 12.3 mmol) in DMF (30 mL) was added HATU (4.67 g, 12.3 mmol) and 3-S-phenyl-1-butanoic acid (2g, 12.2 mmol) and DIPEA (2.12 mL). Stirred over night then poured into water and extracted into ethyl acetate. Dried over $MgSO_4$ and evaporated to afford the title compound as a white solid, (4.17g, 99%); NMR: 1.20 (6H, m), 1.38 (9H, s), 1.65 (2H, m), 2.60 (2H, m), 3.00 (1H, m), 3.15 (1H, q), 3.40 (1H, m), 3.80 (1H, d, broad), 4.20 (1H, m), 6.80 (1H, m), 7.18 (1H, m), 7.24 (4H, m); MS: 347, 291 (– BOC).

Method BI

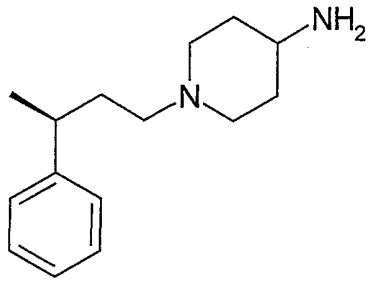
4-Amino-1-(3-S-phenyl-1-butanoic amide)piperidine hydrochloride



To a solution of acetyl chloride (5mL) in methanol (20mL) was added 4-Boc-amino-1-(3-S-phenyl-1-butanoic amide)piperidine(1g, 3mmol) and stirred for one hour. The solvents were then evaporated to afford the title compound as a white solid. (930mg, 100% for HCl salt); NMR: 1.20 (3H, d), 1.35 (2H, m), 1. 41 (1H, m), 1.89 (2H, m), 2.80-3.20 (5H, m), 3.90 (1H, d), 4.30 (1H, d), 7.10 (1H, m), 7.20 (4H, m); MS: 247.

Method BJ

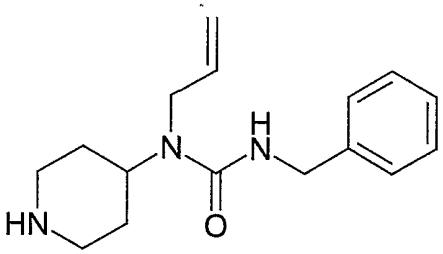
4-Amino-1-(3-**S**-phenylbutyl)piperidine



To a solution of 4-amino-1-(3-**S**-phenyl-1-butanoic amide)piperidine(1g, 3mmol) in THF (20mL) was added a solution of $LiAlH_4$ in THF (10 mL of 1.0M soln) and the mixture was refluxed for 5 hours. The mixture was cooled, quenched with aqueous sodium hydroxide, filtered and the filtrate partitioned between water and ethyl acetate. The combined organic phase was dried, $MgSO_4$, and evaporated to afford the title compound as a white solid. (680 mg, 97 %); NMR: 1.20 (4H, m), 1.60 (4H, m), 1.89 (2H, m), 2.10 (2H, m), 2.43 (1H, m), 2.70 (4H, m), 7.10 (3H, m), 7.20 (2H, m); MS: 233.

Method BK

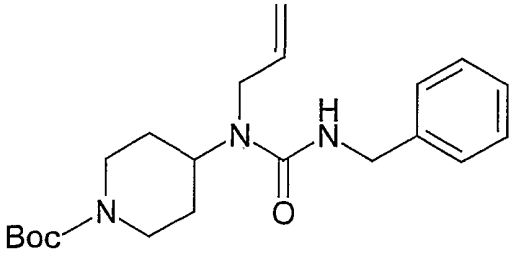
N'-Phenylmethyl-*N*-(4-piperidinyl)-*N*-allylurea hydrochloride



Acetyl chloride (5.5 mL) was added to methanol (20 mL) at 0°C and the mixture stirred for 10 minutes before addition of a solution of *N'*-phenylmethyl-*N*-(1-*tert*-butyloxycarbonyl-4-piperidinyl)-*N*-allylurea (1.54 g, 4.17 mmol) in methanol (1 mL). The resulting mixture was stirred at 0°C for 1 h and at room temperature for 1 h. Evaporation afforded the title compound as a solid (0.96 g); NMR: 1.60 (br d, 2H), 1.93 (m, 2H), 2.80 (m, 2H), 3.10 (m, 2H), 3.79 (d, 2H), 4.21 (m, 3H), 5.10 (d, 1H), 5.18 (dd, 1H), 5.80 (ddt, 1H), 7.20 (m, 5H), 9.21 (br s, 2H); MS: 274.

Method BL

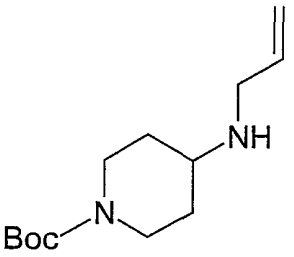
N'-Phenylmethyl-*N*-(1-tert-butoxycarbonyl-4-piperidinyl)-*N*-allylurea



To a stirred solution of 1-tert-butoxycarbonyl-4-allylaminopiperidine (1.0 g, 4.17 mmol) in DCM (20 mL) was added benzylisocyanate (0.52 mL, 4.2 mmol) and the resulting mixture was stirred at room temperature for 20 h. Water was added and the mixture evaporated to yield the title compound (1.54 g, 99%); NMR 1.39 (s, 9H), 1.50 (m, 4H), 2.70 (m, 2H), 3.79 (d, 2H), 4.0 (m, 3H), 4.21 (d, 2H), 5.10 (d, 1H), 5.18 (dd, 1H), 5.90 (ddt, 1H), 6.62 (t, 1H), 7.20 (m, 5H); MS: 274 (MH^+ – BOC).

Method BM

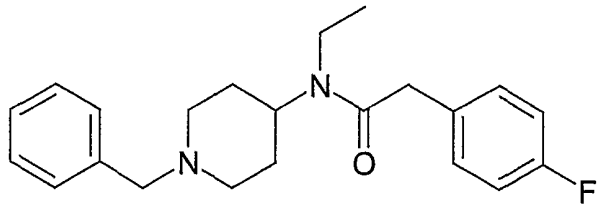
1-tert-Butoxycarbonyl-4-allylaminopiperidine



To a solution of 1-tert-butoxycarbonyl-4-piperidone (10.0 g, 50 mmol) in 1,2-dichloroethane (140 mL) was added allylamine (3.4 g, 60 mmol), acetic acid (3.0 mL) and 3Å molecular sieves (20 g). The resulting mixture was stirred at room temperature for 45 min. Sodium triacetoxyborohydride (16.2 g, 76 mmol) was added and stirring was continued for a further 4 h. The reaction was quenched with water and extracted twice with ethyl acetate. The organic extracts were washed with sodium bicarbonate solution, combined, dried ($MgSO_4$) and concentrated to afford the title compound as an oil (11.5 g, 96%); NMR ($CDCl_3$): 1.21 (m, 2H), 1.40 (s, 9H), 1.60 (br s, 1H), 1.81 (d, 2H), 2.63 (m, 1H), 2.80 (t, 2H), 3.29 (t, 2H), 4.05 (d, 2H), 5.10 (d, 1H), 5.18 (dd, 1H), 5.90 (ddt, 1H).

Method BN

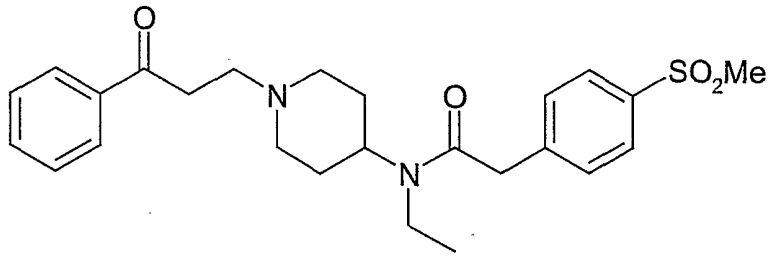
N-(1-Phenylmethyl-4-piperidinyl-*N*-ethyl-4-fluorophenylacetamide



This was prepared by reacting 1-phenylmethyl-4-ethylaminopiperidine dihydrochloride with 4-fluorophenylacetic acid according to the procedure used for Method AJ; NMR (CDCl3): 1.13 and 1.19 (t, 3H), 1.35 and 1.85 (m, 2H), 1.74 and 2.08 (m, 2H), 2.90 (br m, 2H), 3.30 (m, 2H), 3.46 (s, 2H), 3.66 (s, 2H), 3.55 and 4.42 (m, 1H), 7.00 (m, 2H), 7.2 - 7.3 (m, 7H); MS: 355.

Method BO

N-[1-(3-phenyl]-3-oxopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide hydrochloride



To a solution of *N*-(4-piperidinyl)-*N*-ethyl-4-methanesulfonylphenylacetamide (Method AI) (14.8g, 45.8mmol) and DIPEA (24mL, 137mmol) in DMF (250mL) was added 3-chloropropiophenone (7.3g, 43.5mmol). The resulting mixture was stirred at room temperature for 20h. The mixture was evaporated and the residue triturated with 5%MeOH/EtOAc to give a solid which was collected by filtration and washed with EtOAc affording the title compound (16.9g, 75%); NMR (DMSO at 373K): 1.14 (t, 3H), 1.77 (m, 2H), 2.34 (m, 2H), 3.11 (m, 2H), 3.15 (s, 3H), 3.45-3.60 (m, 6H), 3.65 (t, 2H), 3.93 (s, 2H), 4.25 (br m, 1H), 7.53 (m, 4H), 7.65 (m, 1H), 7.84 (d, 2H) and 7.98 (d, 2H); MS: 457.

Method BP

3-(3-Trifluoromethylphenyl)butyraldehyde

Step 1: (*E*)-Ethyl 3-(3-trifluoromethylphenyl)-2-butenoate

To a solution of triethyl phophonoacetate (1.98ml, 10mmol) in THF at 0°C was added lithium bis(trimethylsilyl)amide (12ml 1M in THF, 12mmol) and the resulting mixture stirred

for 10min. 3'-Trifluoromethylacetophenone (1.52ml, 10mmol) was added and the resulting mixture was stirred whilst allowing to warm to room temperature over 1h. The mixture was evaporated and the residue partitioned between water and ethyl acetate, the organic phase was washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by Bond Elut chromatography (eluent isohexane then 1:1 ethyl acetate/isohexane) affording the sub-titled compound (1.4g); NMR ($CDCl_3$): 1.3 (t, 3H), 2.6 (s, 3H), 4.2 (q, 2H), 6.15 (s, 1H), 7.5 (m, 1H), 7.6 (m, 2H), 7.7 (s, 1H).

Step 2: Ethyl 3-(3-trifluoromethylphenyl)butanoate

To a solution of (*E*)-ethyl 3-(3-trifluoromethylphenyl)-2-butenoate (Step 1) (1.4g) in ethyl acetate (50ml) was added 10% Pd/C (140mg) and the resulting mixture was stirred under an atmosphere of hydrogen for 18h. The mixture was filtered through Celite® and the filtrate evaporated to give the sub-titled compound (1.33g); NMR ($CDCl_3$): 1.2 (t, 3H), 1.35 (d, 3H), 2.6 (m, 2H), 3.4 (m, 1H), 4.1 (q, 2H), 7.4 (m, 4H).

Step 3: 3-(3-Trifluoromethylphenyl)butanol

To a solution of ethyl 3-(3-trifluoromethylphenyl)butanoate (Step 2) (1.35g, 5.2mmol) in THF (15ml) at 0°C was added lithium aluminium hydride (5.2ml, 1M in THF, 5.2mmol) and the resulting mixture was stirred for 5min. Ethyl acetate (10ml) was added followed by water (0.2ml) then 6M NaOH solution (0.2ml) then water (2ml) and the resulting mixture stirred at room temperature for 5min. before filtration through Celite®. The filtrate was dried ($MgSO_4$) and evaporated giving the sub-titled compound (1.1g); NMR ($CDCl_3$): 1.3 (d, 3H), 1.9 (m, 2H), 3.0 (m, 1H), 3.6 (m, 2H), 7.4 (m, 4H).

Step 4: 3-(3-Trifluoromethylphenyl)butyraldehyde

To a stirred solution of 3-(3-trifluoromethylphenyl)butanol (Step 3) (1.1g, 5.05mmol) in DCM (10ml) was added Dess-Martin periodinane (2.36g, 5.56mmol) and the resulting mixture stirred at room temperature for 10min. The mixture was washed three times with 2M NaOH solution (20ml), then with brine (20ml), dried ($MgSO_4$) and evaporated giving the title compound (1g, 92%); NMR ($CDCl_3$): 1.34 (d, 3H), 2.75 (m, 2H), 3.43 (m, 1H), 7.46 (m, 4H), 9.73 (s, 1H).

The same sequence of reactions was used to prepare 3-(3-chlorophenyl)butyraldehyde and 3-(3,4-dichlorophenyl)butyraldehyde except that platinum (IV) oxide was used as catalyst in the reduction of (*E*)-ethyl 3-(3-chlorophenyl)-2-butenoate and (*E*)-ethyl 3-(3,4-

dichlorophenyl)-2-butenoate to ethyl 3-(3-chlorophenyl)butanoate and ethyl 3-(3,4-dichlorophenyl)butanoate respectively.

Method BQ

3-Amino-1-(3,3-diphenylpropyl)pyrrolidine di-(trifluoroacetic acid) salt

Step 1: 3-Boc-amino-1-(3,3-diphenylpropyl)pyrrolidine

To a mixture of 3-boc-aminopyrrolidine (1g, 5.4mmol) and 3,3-diphenylpropionaldehyde (1.1g, 5.4mmol) in DCM (20ml) and MeOH (5ml) was added acetic acid (0.1ml) and the resulting mixture stirred at room temperature for 1h. Sodium triacetoxyborohydride (5.4mmol) was added and the mixture stirred for 18h. The reaction mixture was washed twice with water (10ml), dried and evaporated giving the sub-titled compound (2.1g); MS: 381.

Step 2: 3-Amino-1-(3,3-diphenylpropyl)pyrrolidine di-(trifluoroacetic acid) salt

3-Boc-amino-1-(3,3-diphenylpropyl)pyrrolidine (Step 1) (2.1g) was dissolved in trifluoroacetic acid (10ml) and the resulting mixture was stirred at room temperature for 2h then evaporated giving the title compound (2.3g).

Method BR

3-(4-Chlorophenyl)-3-(4-pyridyl)propionaldehyde

Step 1: 3-(4-Chlorophenyl)-3-(4-pyridyl)prop-1-ene

To a solution of 4-(4-chlorobenzyl)pyridine (1g, 4.9mmol) in THF was added n-butyl lithium (3.4ml of 1.6M solution, 5.4mmol) dropwise at room temperature. After stirring for 15min. the mixture was cooled to –78°C and allyl bromide (0.65g, 5.4mmol) was added dropwise. The reaction mixture was stirred while warming to room temperature over 18h. The mixture was purified by Bond Elut chromatography (eluent isohexane then diethyl ether) giving the sub-titled compound as an oil (0.54g); NMR ($CDCl_3$): 2.8 (t, 2H), 4.0 (t, 1H), 5.0 (m, 2H), 5.7 (m, 1H), 7.1 (m, 4H), 7.3 (m, 2H) and 8.5 (m, 2H); MS: 244.

Step 2: 3-(4-Chlorophenyl)-3-(4-pyridyl)propionaldehyde

3-(4-Chlorophenyl)-3-(4-pyridyl)prop-1-ene (Step 1) (0.54g, 2.2mmol) was dissolved in MeOH (30ml) and the solution cooled to –78°C. Ozone was bubbled through until a blue colour persisted (20min.). The mixture was purged with oxygen and dimethyl sulphide

(0.33ml) was added. The mixture was stirred for 1h while warming to room temperature, then evaporated and the crude product used directly in the next reaction.

The same sequence of two reactions was used to prepare 3-(4-chlorophenyl)-3-(2-pyridyl)propionaldehyde.

Method BS

3-(1,3-Benzodioxol-5-yl)-3-phenylpropionaldehyde

Step 1: (*E*)-tert-Butyl 3-(1,3-benzodioxol-5-yl)propenonate

A solution of 3,4-methylenedioxycinnamic acid (0.77g, 4mmol) in toluene (10ml) was heated with stirring to 80°C and N,N-dimethylformamide di-tert-butyl acetal (3.83ml, 16mmol) was added dropwise. The resulting mixture was stirred at 80°C for 2h then cooled to room temperature. The mixture was washed with water and brine, dried (Na_2SO_4) and evaporated. The residue was purified by Bond Elut chromatography (eluent iso-hexane then DCM) giving the sub-titled compound as a solid (0.48g).

Step 2: tert-Butyl 3-(1,3-benzodioxol-5-yl)-3-phenylpropionate

To a –78°C solution of (*E*)-tert-butyl 3-(1,3-benzodioxol-5-yl)propenonate (Step 1) (2.4mmol) in THF (5ml) was added phenyl lithium (2ml of 1.8M solution, 3.6mmol) dropwise and the resulting mixture stirred at –78°C for 2h. Water (5ml) was added and the mixture allowed to warm to room temperature over 18h. The mixture was extracted with ethyl acetate, the organic phase was concentrated and the residue purified by Bond Elut chromatography (eluent iso-hexane then DCM) giving the sub-titled compound as an oil (0.51g).

Step 3: 3-(1,3-Benzodioxol-5-yl)-3-phenylpropionaldehyde

To a –78°C solution of tert-butyl 3-(1,3-benzodioxol-5-yl)-3-phenylpropionate (Step 2) (1.36mmol) in DCM (5ml) was added diisobutylaluminium hydride (3ml 1M solution, 3mmol) dropwise and the resulting mixture stirred at –78°C for 90min. MeOH (3ml) was added slowly and the mixture warmed to room temperature. Citric acid solution (10% aqueous, 5ml) was added, the mixture stirred for 10min. then filtered. The filtrate was dried and evaporated yielding the title compound which was used immediately in the next reaction.

The same sequence of three reactions was used to prepare 3-(4-chlorophenyl)-3-phenylpropionaldehyde, 3-(3,4-dichlorophenyl)-3-phenylpropionaldehyde, 3-(4-methoxyphenyl)-3-phenylpropionaldehyde, 3-(3-chlorophenyl)-3-phenylpropionaldehyde, 3-(4-methylphenyl)-3-phenylpropionaldehyde and 3-(4-trifluoromethylphenyl)-3-phenylpropionaldehyde.

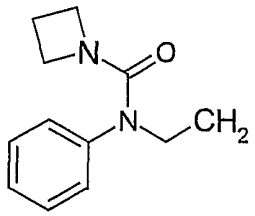
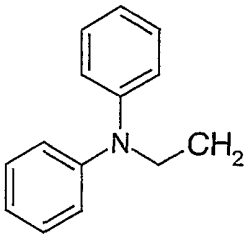
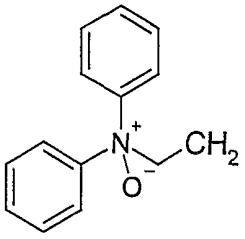
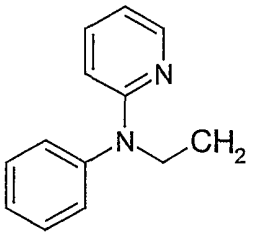
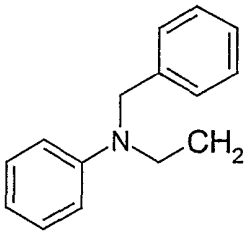
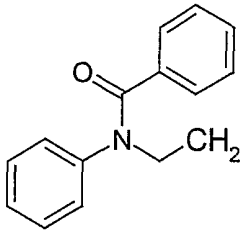
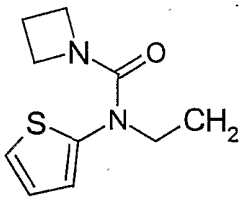
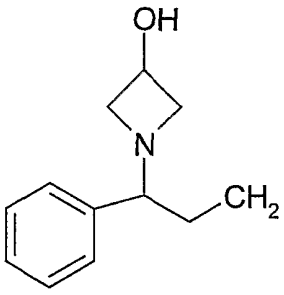
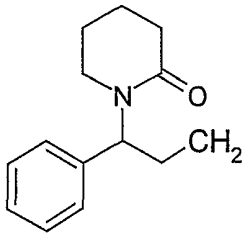
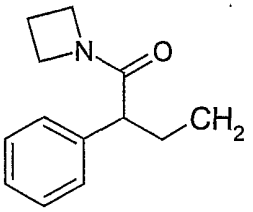
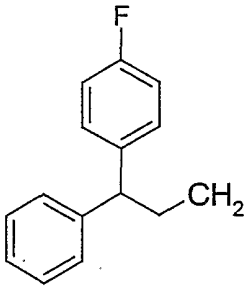
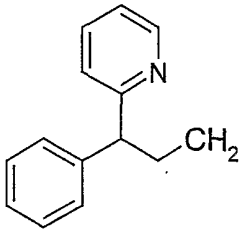
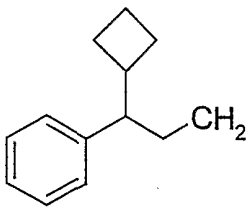
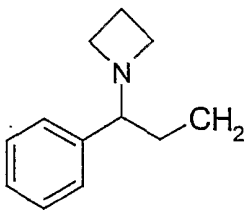
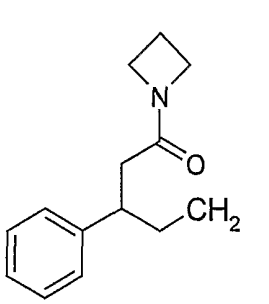
EXAMPLE 34

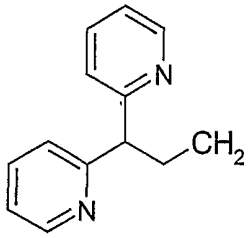
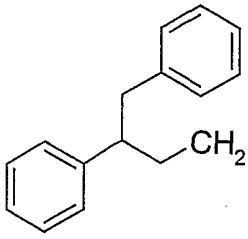
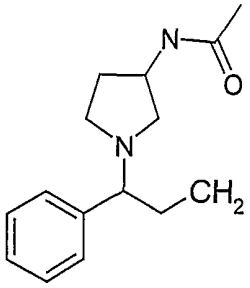
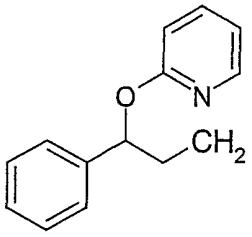
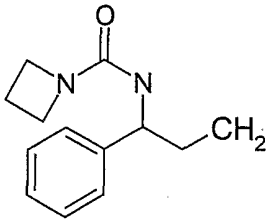
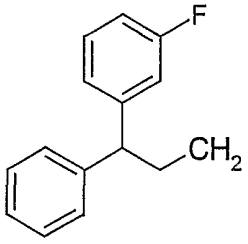
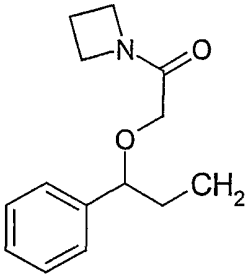
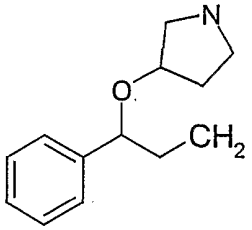
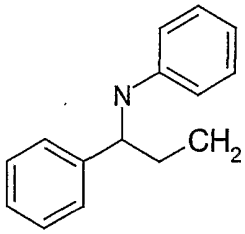
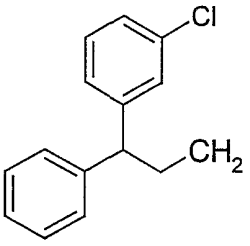
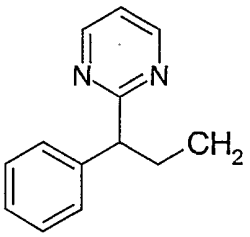
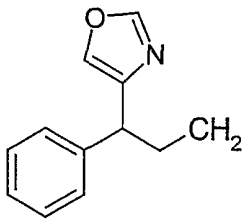
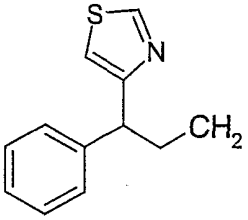
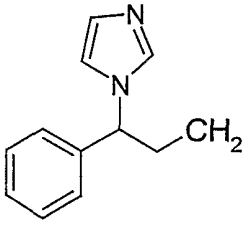
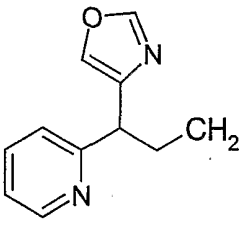
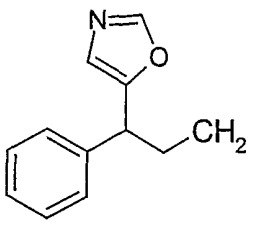
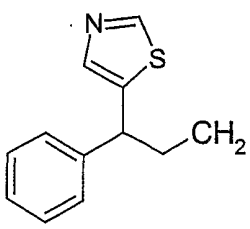
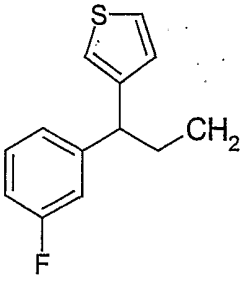
The ability of compounds to inhibit the binding of RANTES was assessed by an *in vitro* radioligand binding assay. Membranes were prepared from Chinese hamster ovary cells which expressed the recombinant human CCR5 receptor. These membranes were incubated with 0.1nM iodinated RANTES, scintillation proximity beads and various concentrations of the compounds of the invention in 96-well plates. The amount of iodinated RANTES bound to the receptor was determined by scintillation counting. Competition curves were obtained for compounds and the concentration of compound which displaced 50% of bound iodinated RANTES was calculated (IC_{50}). Preferred compounds of formula (I) have an IC_{50} of less than 50μM.

EXAMPLE 35

The ability of compounds to inhibit the binding of MIP-1α was assessed by an *in vitro* radioligand binding assay. Membranes were prepared from Chinese hamster ovary cells which expressed the recombinant human CCR5 receptor. These membranes were incubated with 0.1nM iodinated MIP-1α , scintillation proximity beads and various concentrations of the compounds of the invention in 96-well plates. The amount of iodinated MIP-1α bound to the receptor was determined by scintillation counting. Competition curves were obtained for compounds and the concentration of compound which displaced 50% of bound iodinated MIP-1α was calculated (IC_{50}). Preferred compounds of formula (I) have an IC_{50} of less than 50μM.

SCHEDULE I

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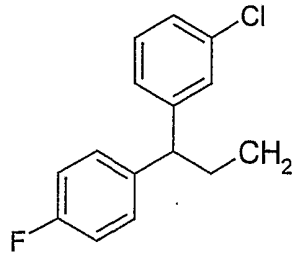
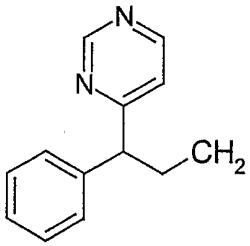
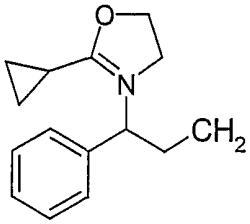
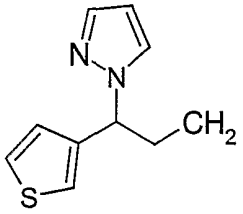
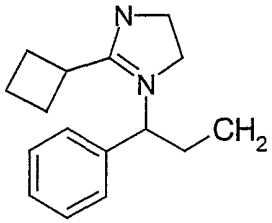
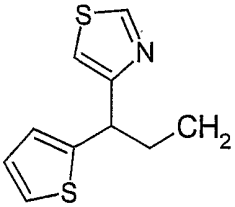
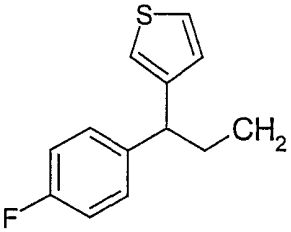
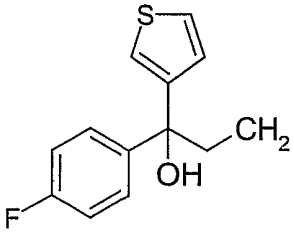
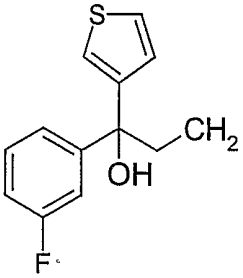
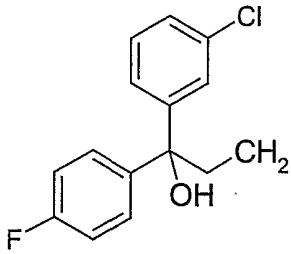
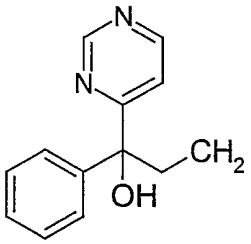
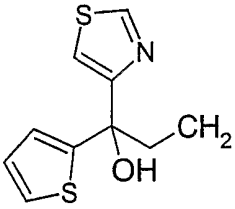
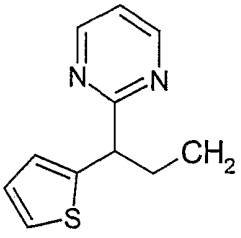
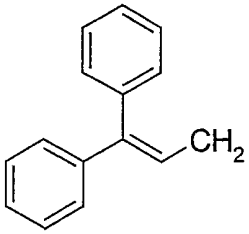
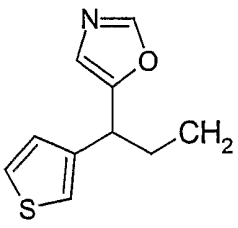
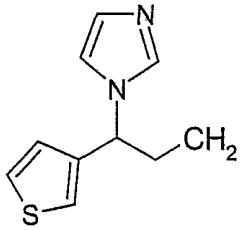
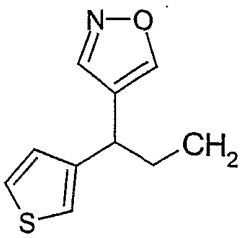
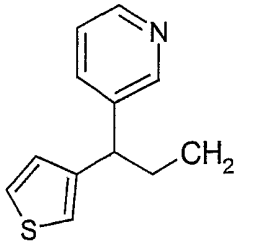

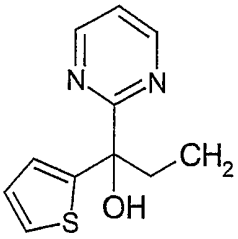
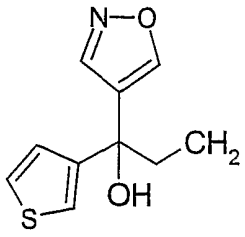
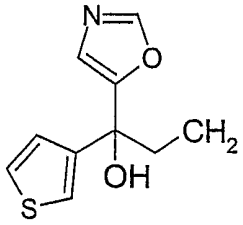
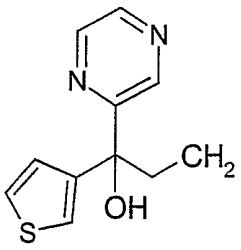
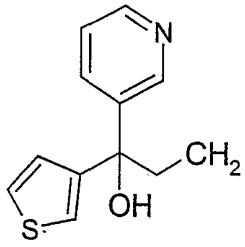
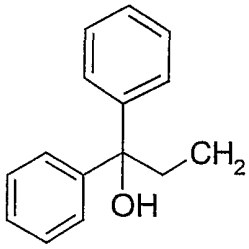
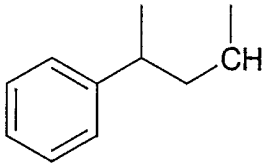
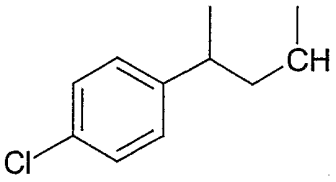
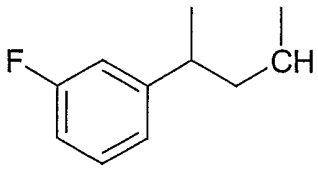
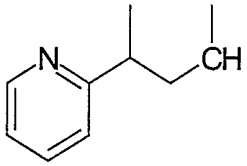
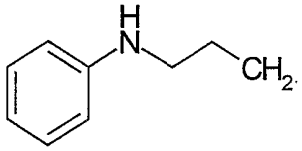
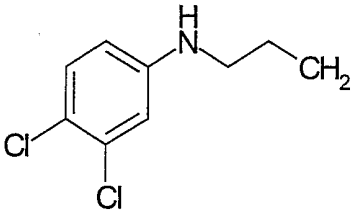
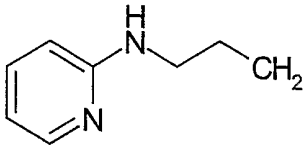
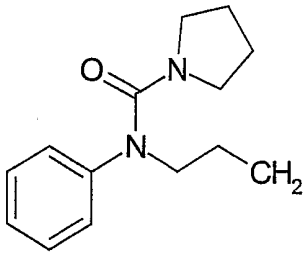
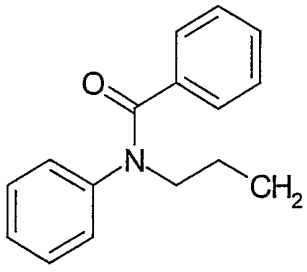
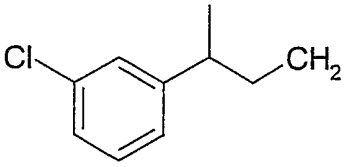
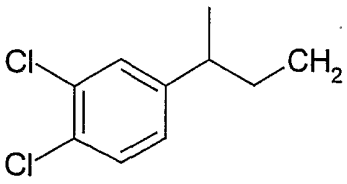
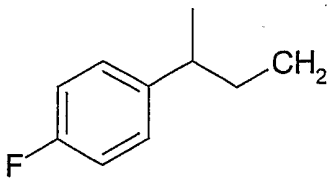

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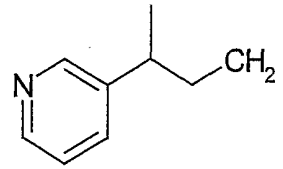
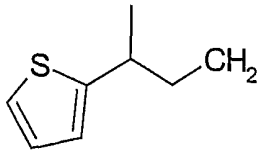
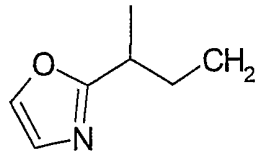
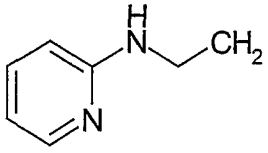
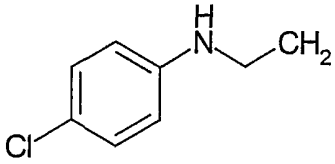
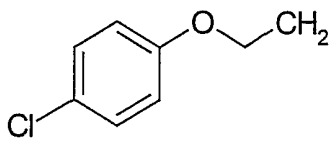
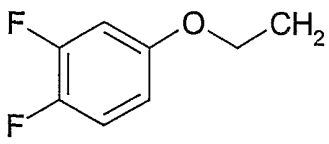
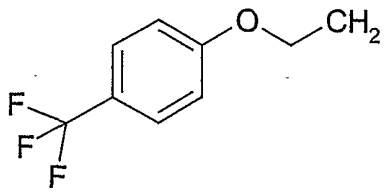
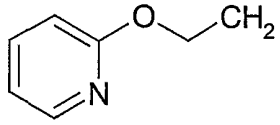
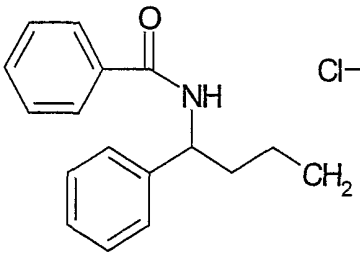
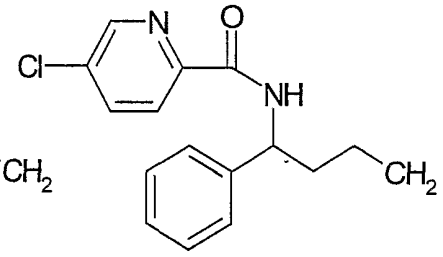
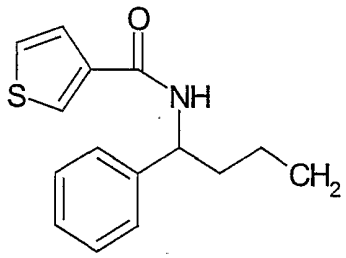
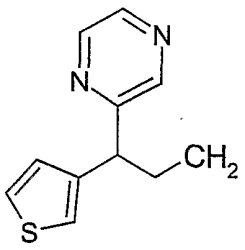

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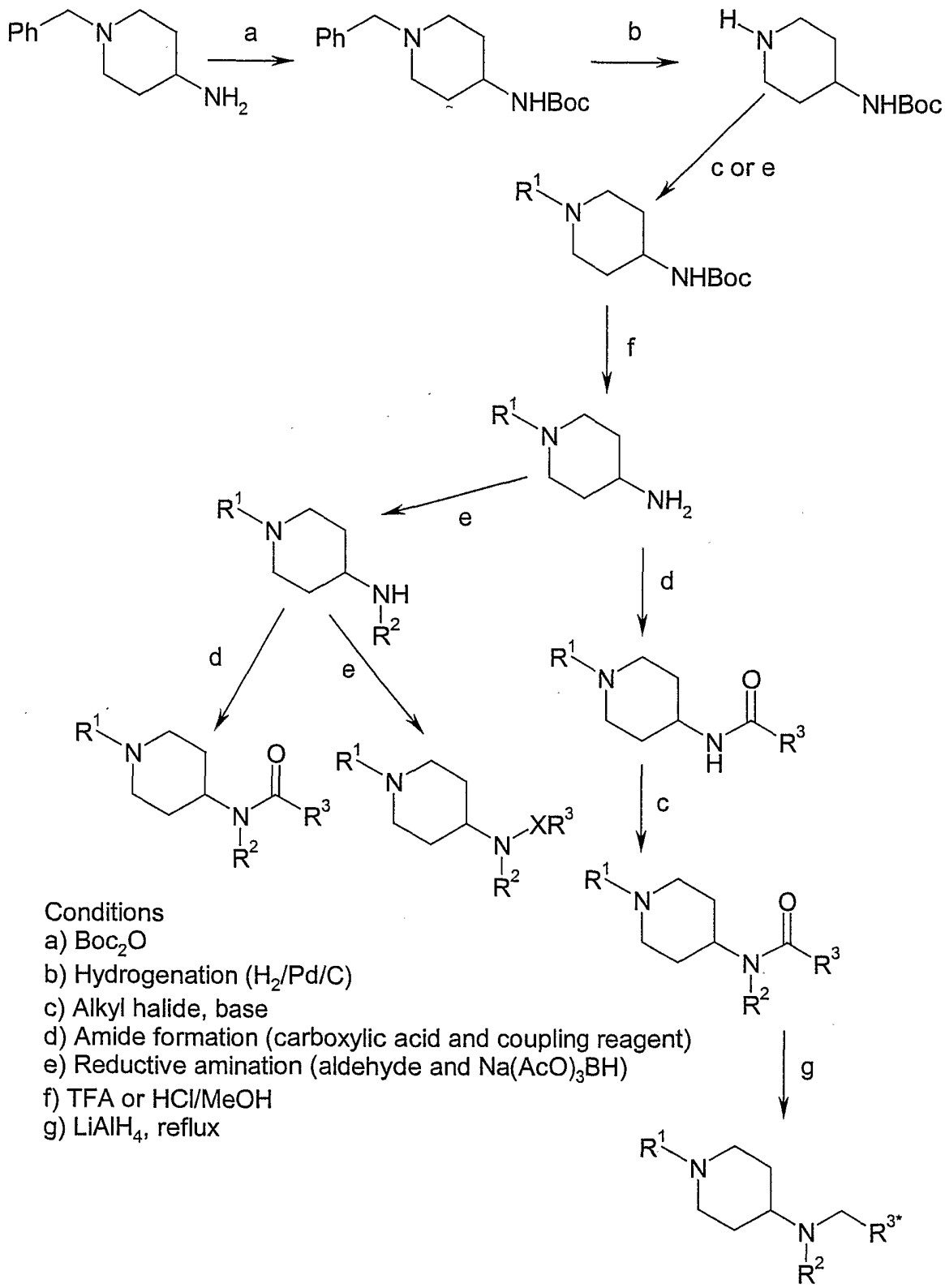
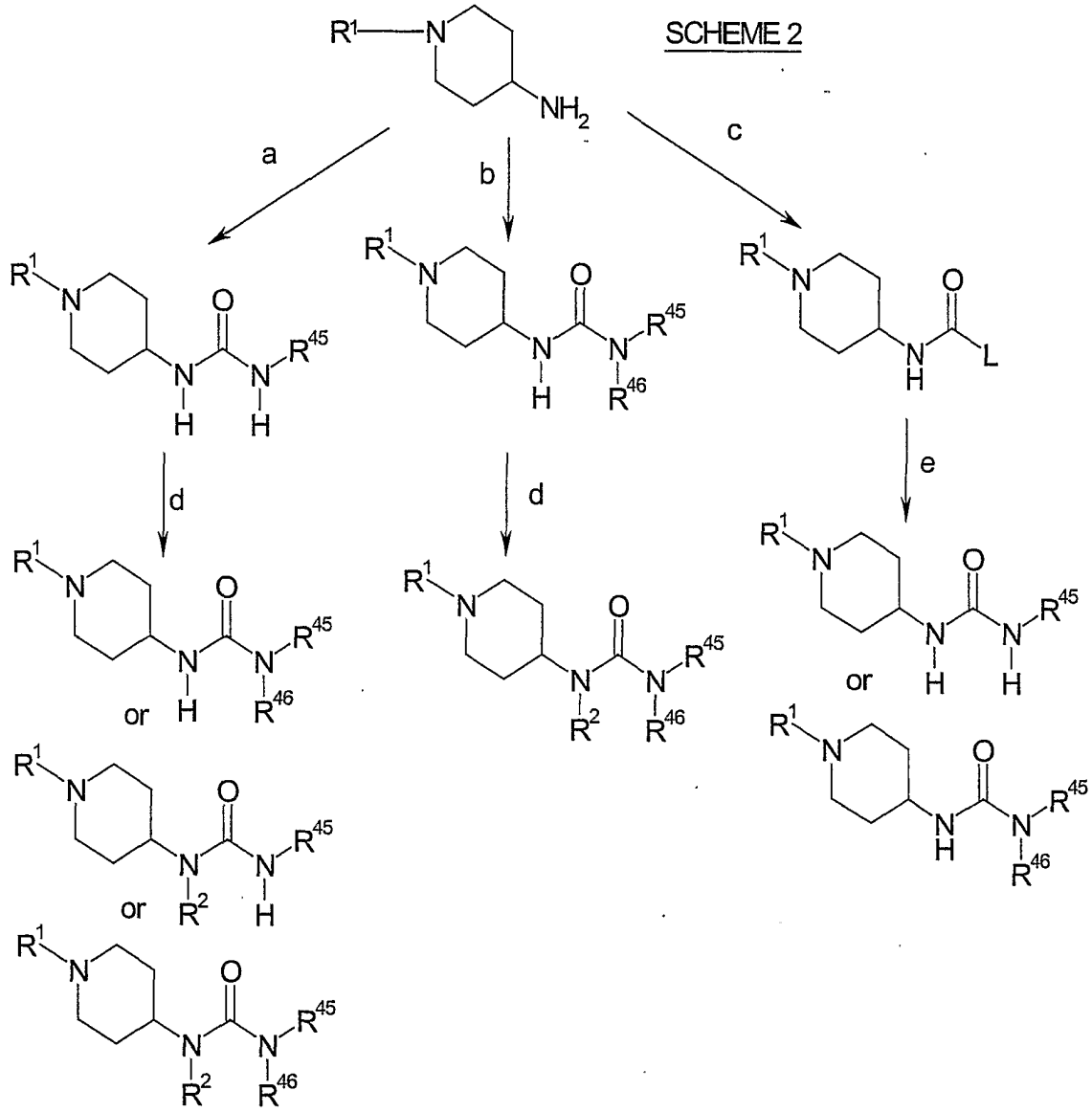
SCHEME 1



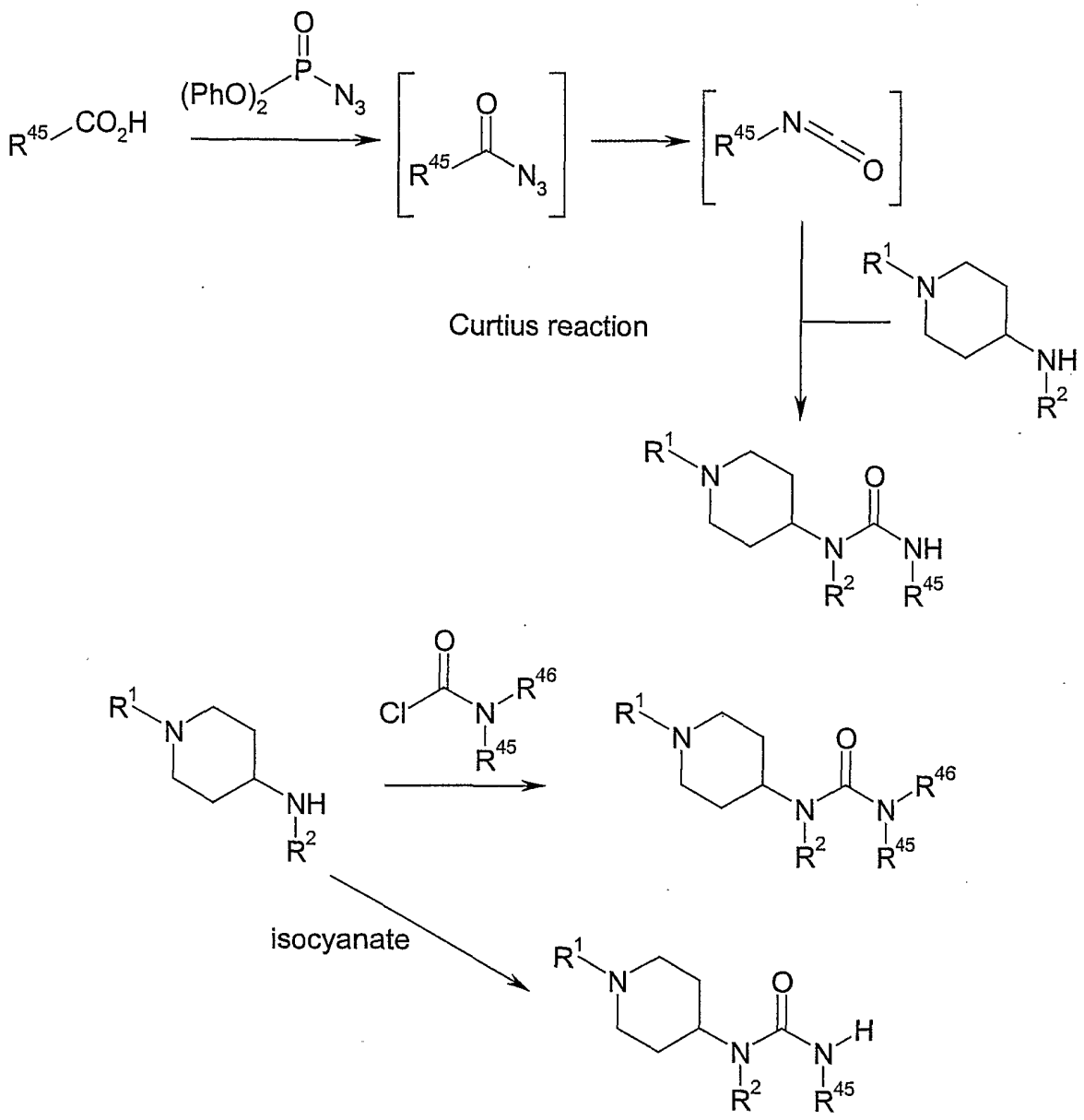
Conditions
a) Boc_2O
b) Hydrogenation (H_2/Pd/C)
c) Alkyl halide, base
d) Amide formation (carboxylic acid and coupling reagent)
e) Reductive amination (aldehyde and $Na(AcO)_3BH$)
f) TFA or HCl/MeOH
g) $LiAlH_4$, reflux

SCHEME 2

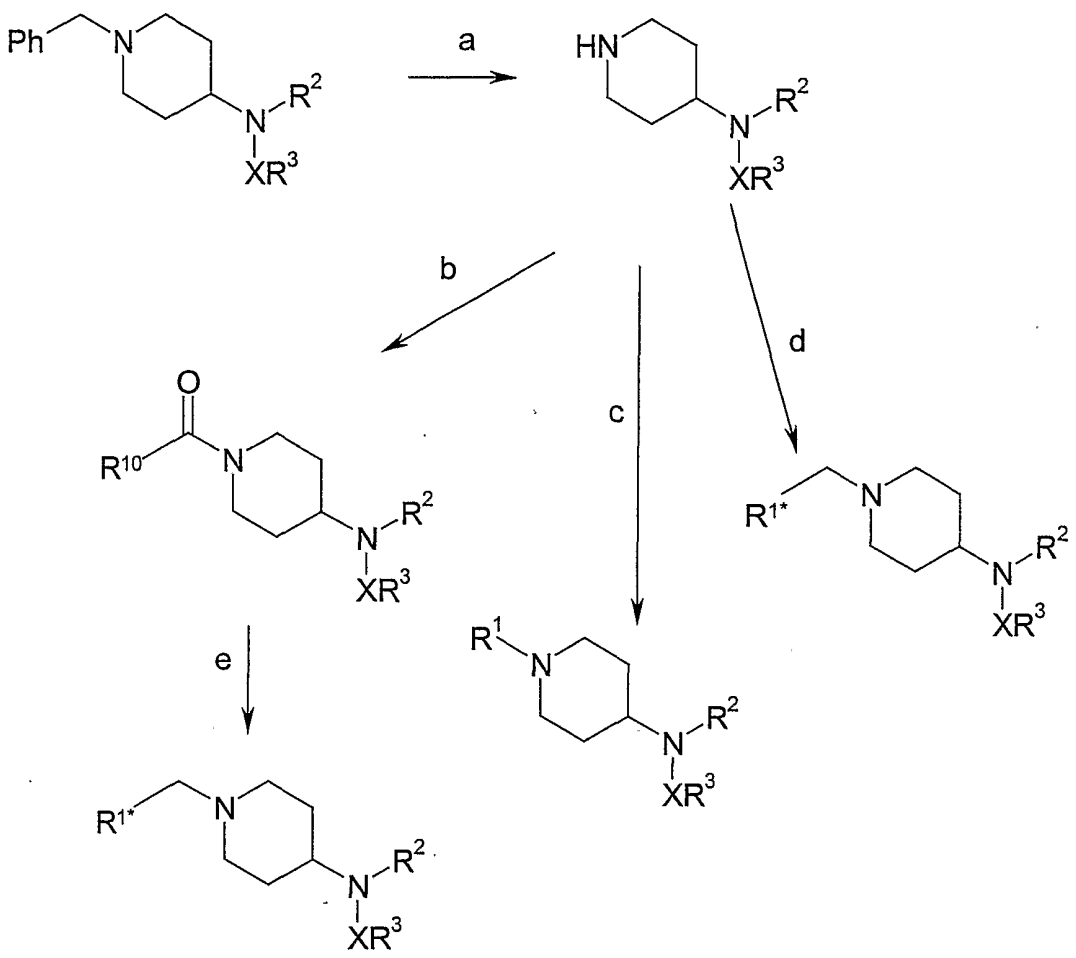


Conditions
a) an isocyanate
b) a carbamoyl chloride
c) phosgene or carbonyldiimidazole
(L = leaving group, eg chloro or imidazolyl)
d) alkyl halide, base
e) a primary or secondary amine
f) $LiAlH_4$, heat
g) Amide formation
h) Reductive amination

SCHEME 3

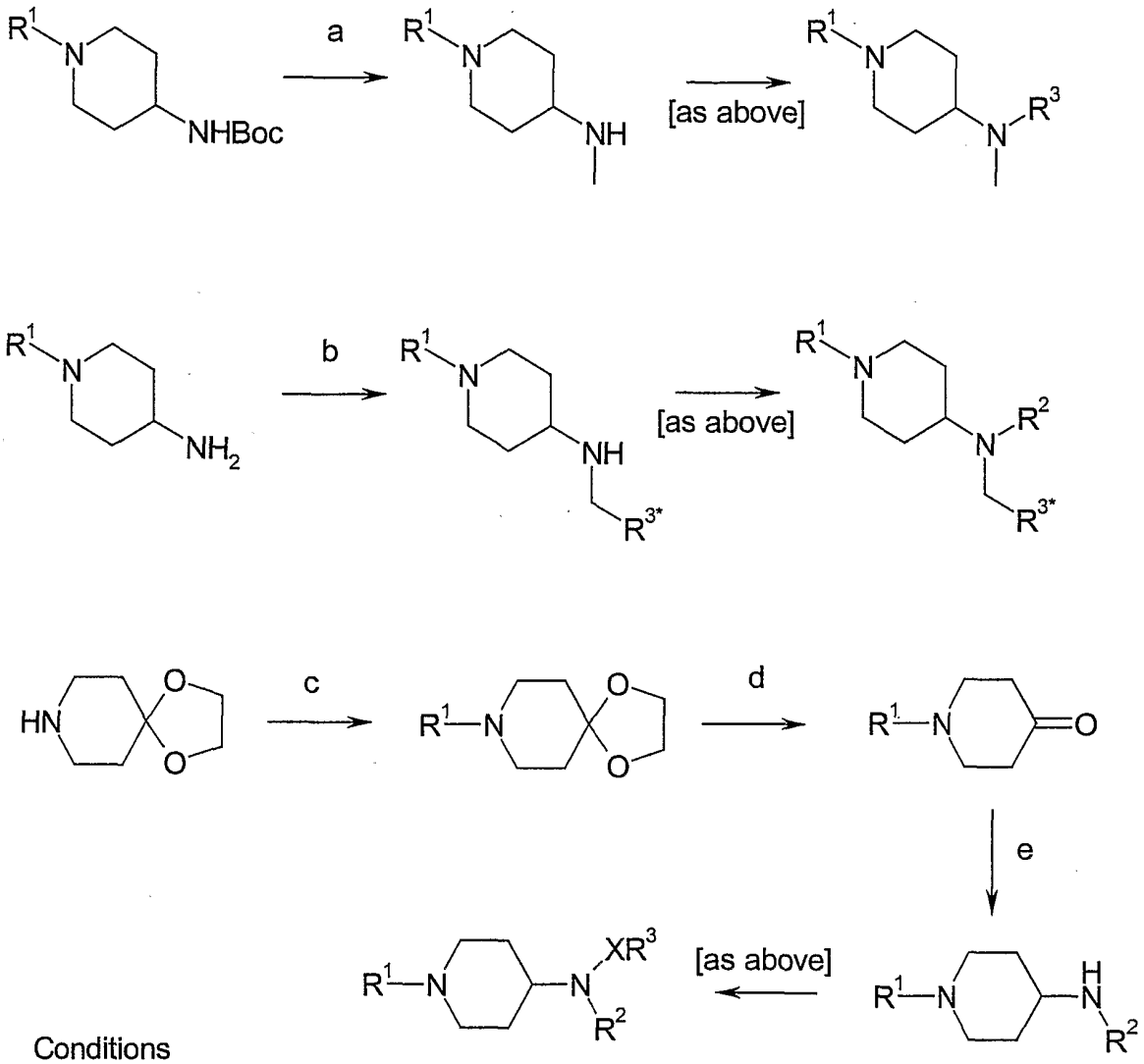


SCHEME 4

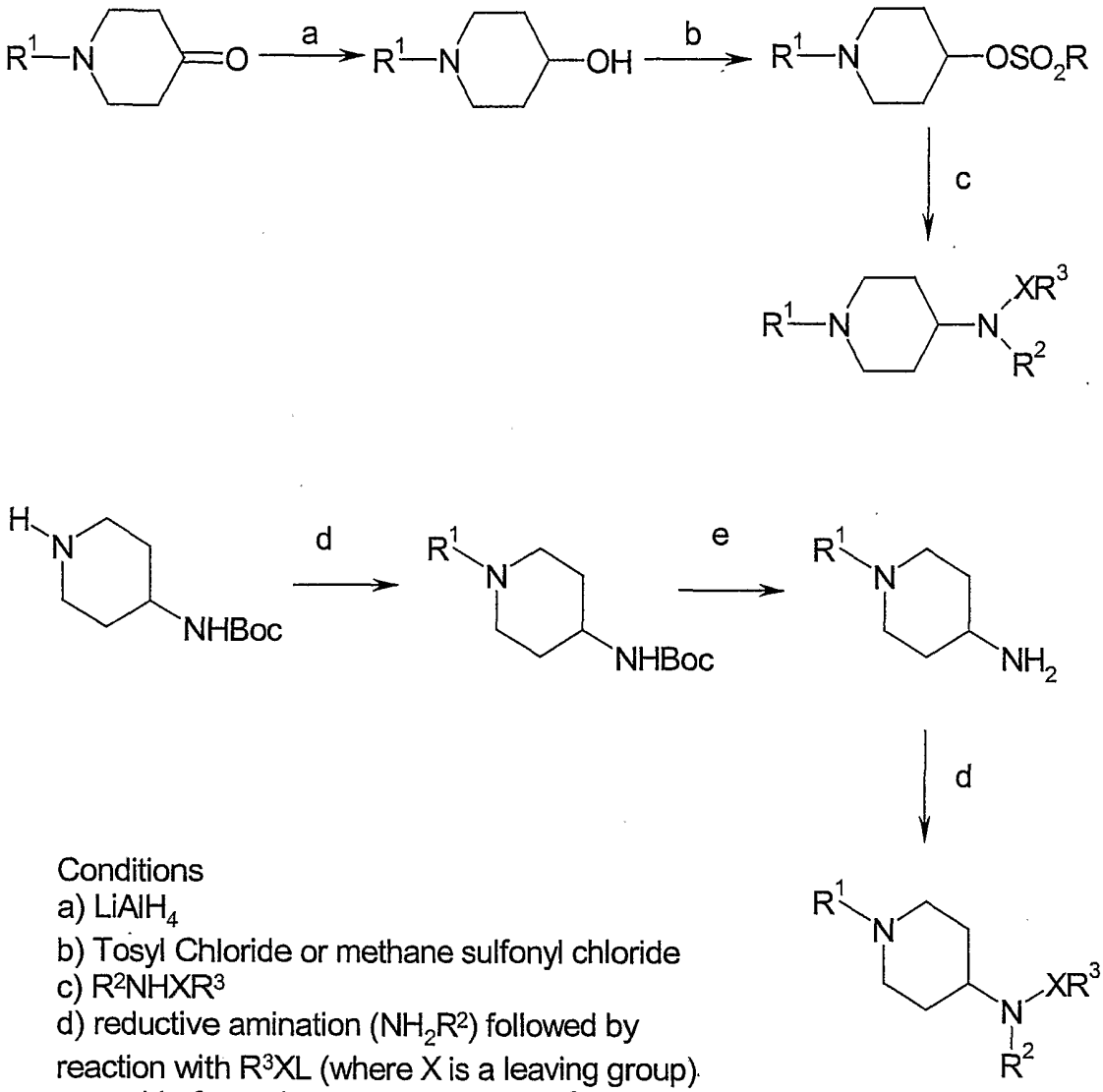


Conditions
a) Hydrogenation (Pd/C)
b) Amide formation ($R^{10}CO_2H$, coupling agent)
c) Alkyl halide, base
d) Reductive amination (aldehyde and $Na(AcO)_3BH$)
e) $LiAlH_4$, heat

SCHEME 5

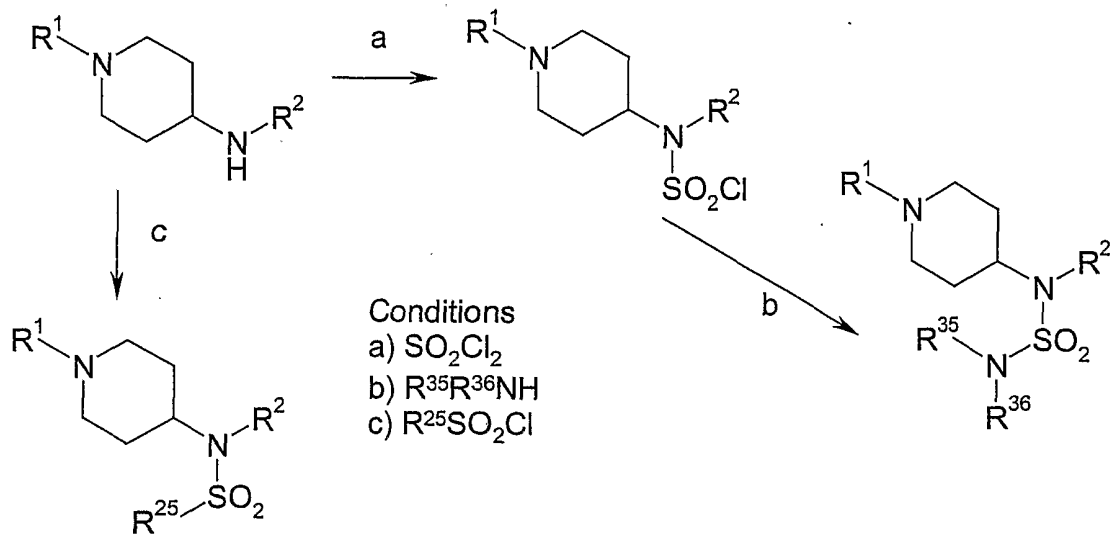

a
[as above]
b
[as above]
c
d
e
[as above]
Conditions
a) LiAlH4, heat
b) Reductive amination (RCHO, Na(AcO)3BH)
c) alkylation
or reductive amination
or amide formation followed by reduction
d) 6M HCl, reflux
e) reductive amination (NH2R2, Na(AcO)3BH

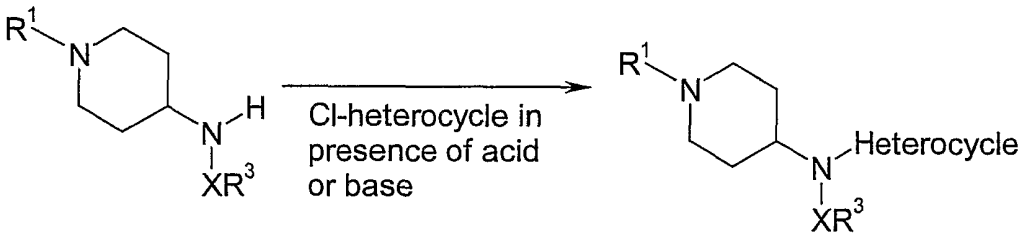
SCHEME 6



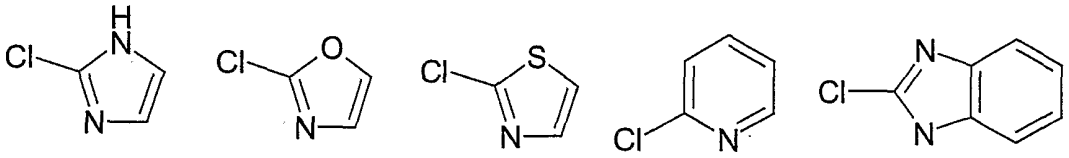
Conditions
a) $LiAlH_4$
b) Tosyl Chloride or methane sulfonyl chloride
c) R^2NHXR^3
d) reductive amination (NH_2R^2) followed by reaction with R^3XL (where X is a leaving group) eg amide formation or reaction with R^3SO_2Cl
e) TFA or MeOH/HCl

SCHEME 7

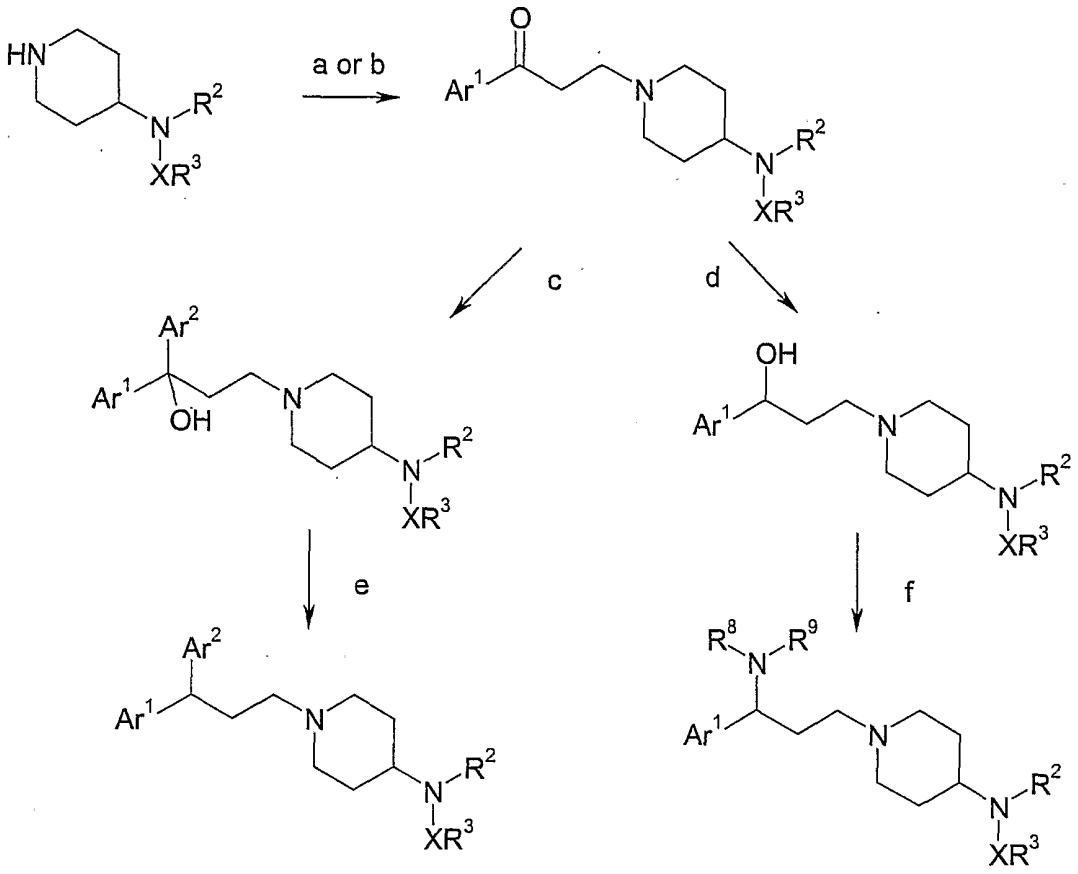




Cl-Heterocycle can include:

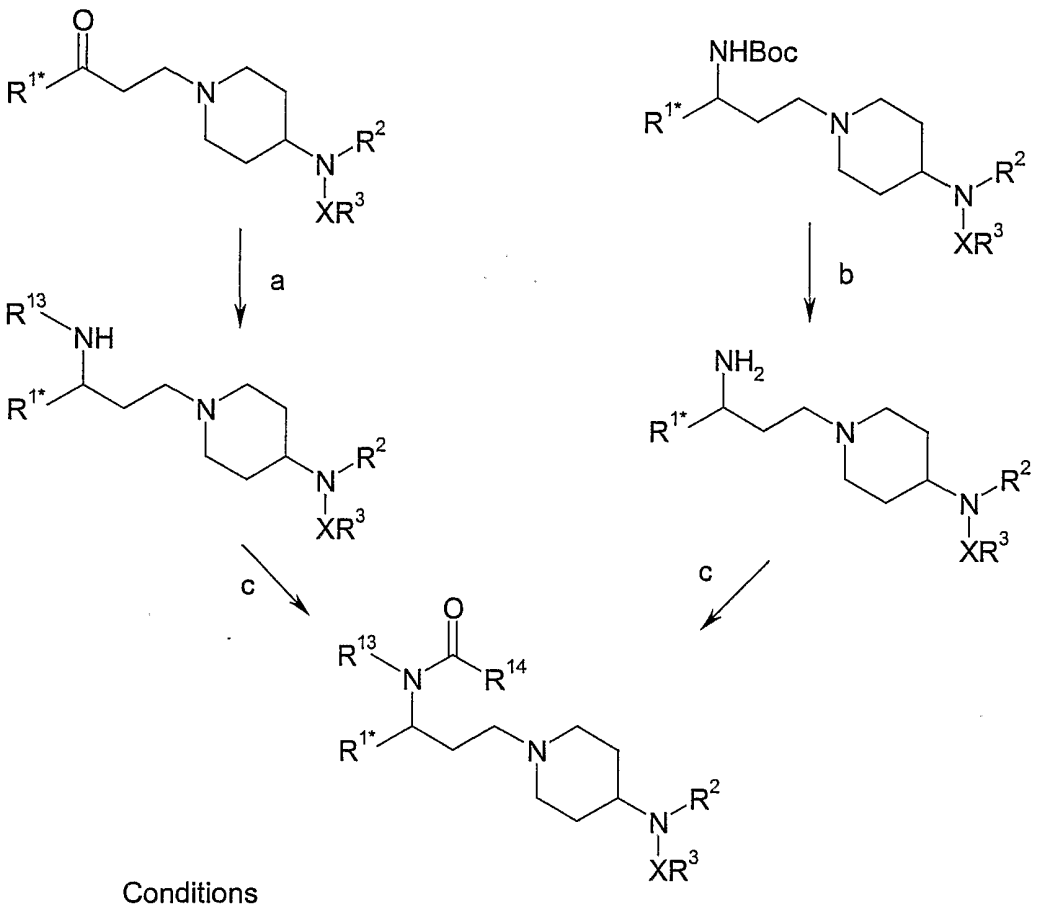


SCHEME 8



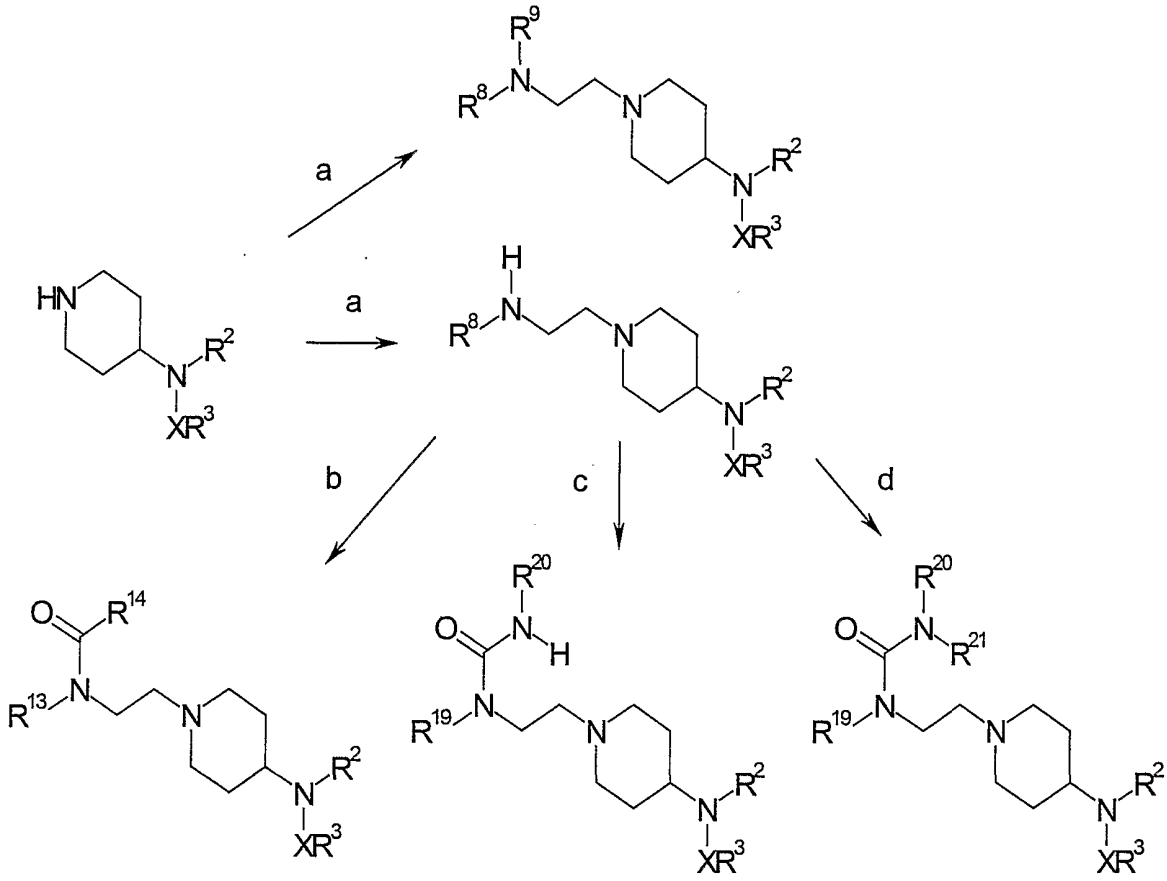
Conditions
a) Alkyl halide, base
b) $Ar^1C(=O)CH_3$, CH_2O, Acetic acid
c) Aryl magnesium halide or Aryl lithium addition
d) Reduction ($NaBH_4$)
e) Reduction (H_2/Pd/C)
f) (i) Activation of OH ($MeSO_2Cl$), (ii) Displacement with R^8R^9NH

SCHEME 9



Conditions
a) Reductive amination ($R^{13}NH_2$, $Na(OAc)_3BH$)
b) TFA or HCl/MeOH
c) Amide formation (carboxylic acid, coupling agent or acid chloride)

SCHEME 10



Conditions:

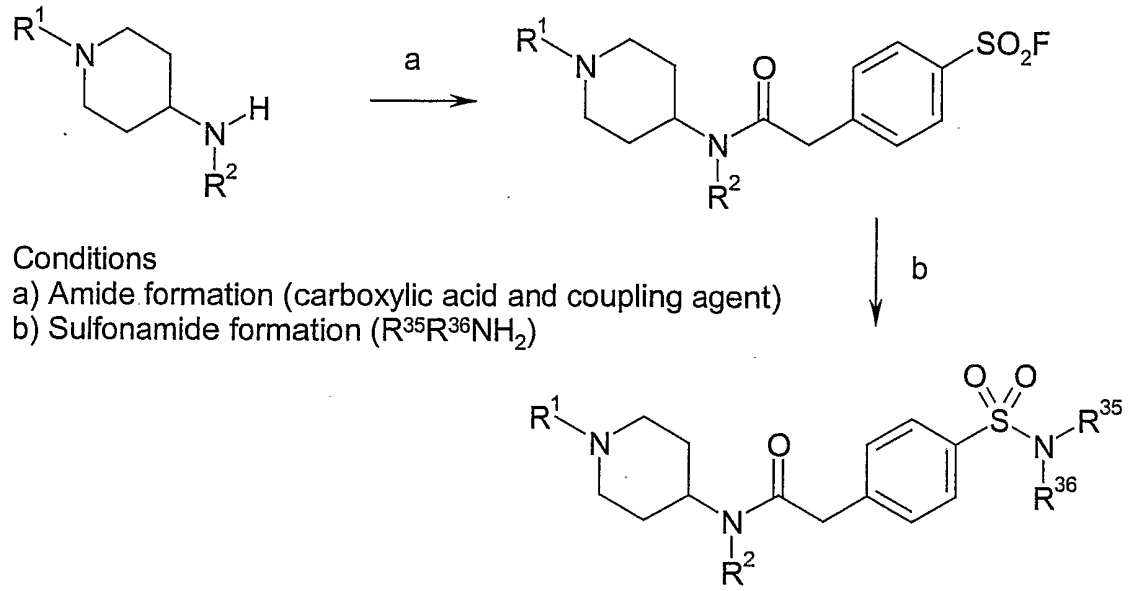
a) Alkyl halide, base

b) Amide formation ($R^{14}CO_2H$, coupling agent or $R^{14}COCl$)

c) an isocyanate

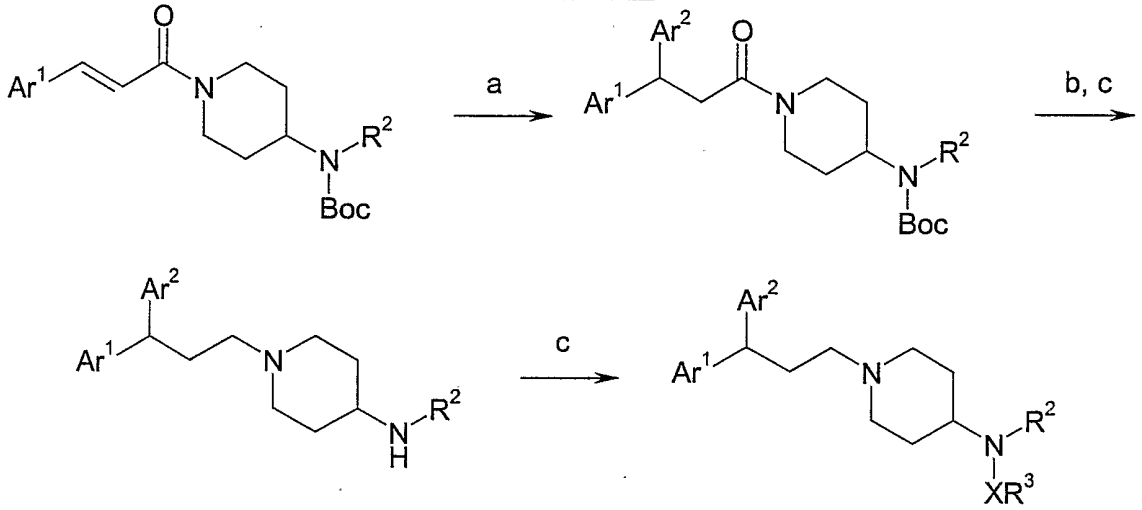
d) a carbamoyl chloride

SCHEME 11



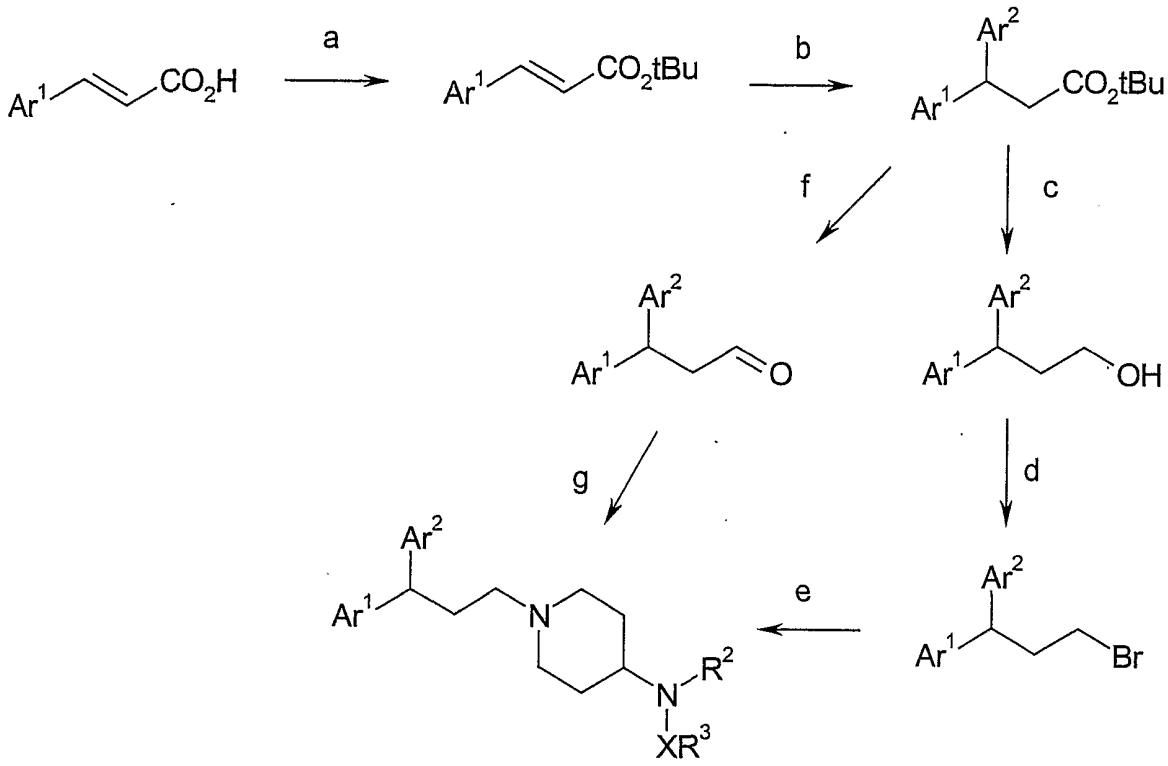
Conditions
a) Amide formation (carboxylic acid and coupling agent)
b) Sulfonamide formation ($R^{35}R^{36}NH_2$)

SCHEME 12



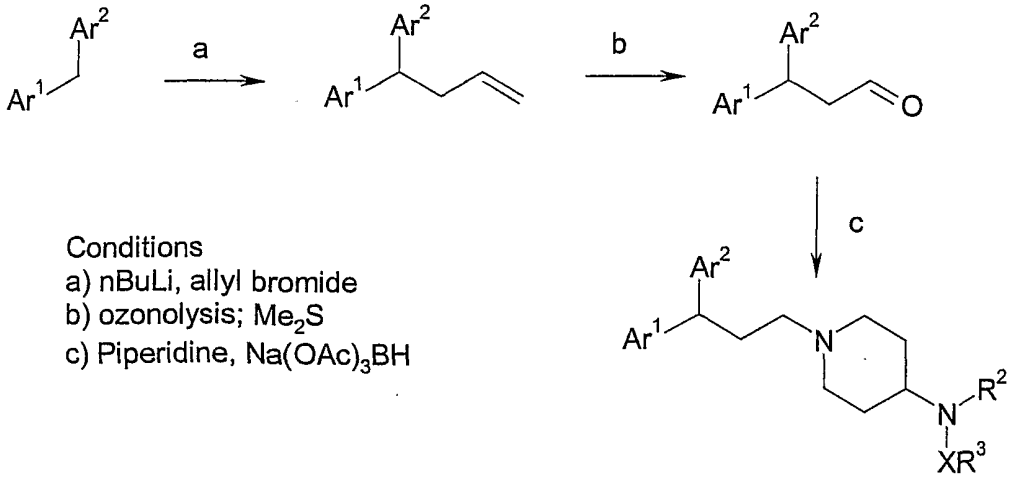
Conditions
a) Ar^2Li
b) TFA or HCl/MeOH
c) Amide reduction (e.g. $LiAlH_4$)
d) Piperidine, $Na(OAc)_3BH$

SCHEME 13



Conditions
a) Ester formation ($Me_2NCH(OtBu)_2$)
b) Aryl lithium addition
c) Ester reduction ($LiAlH_4$)
d) Bromide formation (PPh_3, CBr_4)
e) Piperidine, base
f) Ester reduction (DIBAL-H)
g) Piperidine, $Na(OAc)_3BH$

SCHEME 14

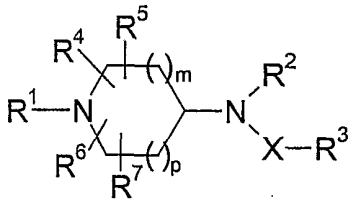


Conditions
a) nBuLi, allyl bromide
b) ozonolysis; Me_2S
c) Piperidine, $Na(OAc)_3BH$

5

CLAIMS

1. A compound of formula (I):



(I)

wherein:

R^1 is C_{1-6} alkyl , C_{3-7} cycloalkyl, C_{3-8} alkenyl or C_{3-8} alkynyl, each optionally substituted with one or more of: halo, hydroxy, cyano, nitro, C_{3-7} cycloalkyl, NR^8R^9, $C(O)R^{10}$, $NR^{13}C(O)R^{14}$, $C(O)NR^{17}R^{18}$, $NR^{19}C(O)NR^{20}R^{21}$, $S(O)_nR^{22}$, C_{1-6} alkoxy (itself optionally substituted by heterocyclyl or $C(O)NR^{23}R^{24}$), heterocyclyl, heterocyclyloxy, aryl, aryloxy, heteroaryl or heteroaryloxy;

R^2 is hydrogen, C_{1-8} alkyl, C_{3-8} alkenyl, C_{3-8} alkynyl, C_{3-7} cycloalkyl, aryl, heteroaryl, heterocyclyl, aryl(C_{1-4})alkyl, heteroaryl(C_{1-4})alkyl or heterocyclyl(C_{1-4})alkyl;

R^3 is C_{1-8} alkyl, C_{2-8} alkenyl, $NR^{45}R^{46}$, C_{2-8} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(C_{1-4})alkyl, heteroaryl(C_{1-4})alkyl or heterocyclyl(C_{1-4})alkyl;

R^{46} is C_{1-8} alkyl, C_{3-8} alkenyl, C_{3-8} alkynyl, C_{3-7} cycloalkyl, aryl, heteroaryl, heterocyclyl, aryl(C_{1-4})alkyl, heteroaryl(C_{1-4})alkyl or heterocyclyl(C_{1-4})alkyl;

wherein the groups of R^2, R^3 and R^{46}, and the heterocyclyl, aryl and heteroaryl moieties of R^1, are independently optionally substituted by one or more of halo, cyano, nitro, hydroxy, $S(O)_qR^{25}$, $OC(O)NR^{26}R^{27}$, $NR^{28}R^{29}$, $NR^{30}C(O)R^{31}$, $NR^{32}C(O)NR^{33}R^{34}$, $S(O)_2NR^{35}R^{36}$, $NR^{37}S(O)_2R^{38}$, $C(O)NR^{39}R^{40}$, $C(O)R^{41}$, CO_2R^{42}, $NR^{43}CO_2R^{44}$, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, phenyl, phenyl(C_{1-4})alkyl, phenoxy, phenylthio, phenyl(C_{1-4})alkoxy, heteroaryl, heteroaryl(C_{1-4})alkyl, heteroaryloxy or heteroaryl(C_{1-4})alkoxy; wherein any of the immediately foregoing phenyl and heteroaryl moieties are optionally substituted with halo, hydroxy, nitro, $S(O)_kC_{1-4}$ alkyl, $S(O)_2NH_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3; the C_{3-7} cycloalkyl, aryl, heteroaryl and heterocyclyl moieties of

R^1, R^2 and R^3 being additionally optionally substituted with C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl or C_{1-6} alkoxy(C_{1-6})alkyl;

R^4, R^5, R^6 and R^7 are, independently, hydrogen, C_{1-6} alkyl {optionally substituted by halo, cyano, hydroxy, C_{1-4} alkoxy, OCF_3, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $NHC(O)(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$C(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$S(O)_2(C_{1-4}$ alkyl), $CO_2(C_{1-4}$ alkyl), $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, $C(O)NH_2$, CO_2H, $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, heterocyclyl or C(O)(heterocyclyl)}, $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, $C(O)(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl) or C(O)(heterocyclyl); or two of R^4, R^5, R^6 and R^7 can join to form, together with the ring to which they are attached, a bicyclic ring system; or two of R^4, R^5, R^6 and R^7 can form an endocyclic bond (thereby resulting in an unsaturated ring system);

X is C(O), $S(O)_2$, C(O)C(O), a direct bond or $C(O)C(O)NR^{47}$;

k, m, n, p and q are, independently, 0, 1 or 2;

R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43} and R^{44} are, independently, C_{1-8} alkyl, C_{3-8} alkenyl, C_{3-8} alkynyl, C_{3-7} cycloalkyl, aryl, heteroaryl or heterocyclyl each or which is optionally substituted by halo, cyano, nitro, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, SCH_3, $S(O)CH_3$, $S(O)_2CH_3$, NH_2, $NHCH_3$, $N(CH_3)_2$, $NHC(O)NH_2$, $C(O)NH_2$, $NHC(O)CH_3$, $S(O)_2N(CH_3)_2$, $S(O)_2NHCH_3$, CF_3, CHF_2, CH_2F, CH_2CF_3 or OCF_3; and R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43} and R^{44} may additionally be hydrogen;

R^8, R^9, R^{10}, R^{13}, R^{14}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{23}, R^{24}, R^{45} and R^{47} are, independently, hydrogen, alkyl {optionally substituted by halo, hydroxy, C_{1-6} alkoxy, C_{1-6} haloalkoxy, heterocyclyl or phenyl (itself optionally substituted by halo, hydroxy, cyano, C_{1-4} alkyl or C_{1-4} alkoxy)}, phenyl (itself optionally substituted by halo, hydroxy, nitro, $S(O)_kC_{1-4}$ alkyl, $S(O)_2NH_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3) or heteroaryl (itself optionally substituted by halo, hydroxy, nitro, $S(O)_kC_{1-4}$ alkyl, $S(O)_2NH_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3);

R^{22} is alkyl {optionally substituted by halo, hydroxy, C_{1-6} alkoxy, C_{1-6} haloalkoxy, heterocyclyl or phenyl (itself optionally substituted by halo, hydroxy, cyano, C_{1-4} alkyl or C_{1-4} alkoxy)}, phenyl (itself optionally substituted by halo, hydroxy, cyano, C_{1-4} alkyl or C_{1-4} alkoxy) or heteroaryl (itself optionally substituted by halo, hydroxy, cyano, C_{1-4} alkyl or C_{1-4} alkoxy);

the pairs of substituents: R^8 and R^9, R^{13} and R^{14}, R^{17} and R^{18}, R^{20} and R^{21}, R^{23} and R^{24}, R^{26} and R^{27}, R^{28} and R^{29}, R^{30} and R^{31}, R^{32} with either R^{33} or R^{34}, R^{33} and R^{34}, R^{35} and R^{36}, R^{37} and R^{38}, R^{39} and R^{40} and R^{43} and R^{44} may, independently, join to form a ring and such a ring may also comprise an oxygen, sulphur or nitrogen atom;

where for any of the foregoing heterocyclic groups having a ring –N(H)- moiety, that –N(H)- moiety may be optionally substituted by C_{1-4} alkyl (itself optionally substituted by hydroxy), C(O)(C_{1-4} alkyl), C(O)NH(C_{1-4} alkyl), C(O)N(C_{1-4} alkyl)$_2$ or S(O)$_2$(C_{1-4} alkyl);

a ring nitrogen and/or sulphur atom is optionally oxidised to form an *N*-oxide and/or an *S*-oxide;

foregoing heteroaryl or heterocyclyl rings are *C*- or, where possible, *N*-linked;

or a pharmaceutically acceptable salt thereof or a solvate thereof.

2. A compound as claimed in claim 1 wherein heteroaryl is pyrrolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, thienyl, furyl, quinolinyl, isoquinolinyl, dihydroisoquinolinyl, indolyl, benzimidazolyl, benzo[b]furyl, benzo[b]thienyl, phthalazinyl, indanyl, oxadiazolyl or benzthiazolyl.

3. A compouind as claimed in claim 1 or 2 wherein aryl is phenyl.

4. A compound as claimed in claim 1, 2 or 3 wherein heterocyclyl is piperidinyl, morpholinyl, pyrrolidinyl, piperazinyl or tetrahydrofuryl.

5. A compound as claimed in claim 1, 2, 3 or 4 wherein R^4, R^5, R^6 and R^7 are all hydrogen.

6. A compound as claimed in claim 1, 2, 3, 4, or 5 wherein X is C(O).

7. A compound as claimed in claim 1, 2, 3, 4, 5 or 6 wherein m and p are both 1.

8. A compound as claimed in claim 1, 2, 3, 4, 5, 6 or 7 wherein R^2 is methyl, ethyl, allyl, cyclopropyl or propargyl.

9. A compound as claimed in claim 1, 2, 3, 4, 5, 6, 7 or 8 wherein R^3 is $NR^{45}R^{46}$, aryl, heteroaryl, aryl(C_{1-4})alkyl or heteroaryl(C_{1-4})alkyl; R^{45} is hydrogen or C_{1-6} alkyl; R^{46} is aryl, heteroaryl, aryl(C_{1-4})alkyl or heteroaryl(C_{1-4})alkyl; wherein the aryl and heteroaryl groups of R^3 and R^{46} are independently substituted by $S(O)_qR^{25}$, $OC(O)NR^{26}R^{27}$, $NR^{32}C(O)NR^{33}R^{34}$ or $C(O)R^{41}$, and optionally further substituted by one or more of halo, cyano, nitro, hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy(C_{1-6})alkyl, $S(O)_qR^{25}$, $OC(O)NR^{26}R^{27}$, $NR^{28}R^{29}$, $NR^{30}C(O)R^{31}$, $NR^{32}C(O)NR^{33}R^{34}$, $S(O)_2NR^{35}R^{36}$, $NR^{37}S(O)_2R^{38}$, $C(O)NR^{39}R^{40}$, $C(O)R^{41}$, CO_2R^{42}, $NR^{43}CO_2R^{44}$, C_{3-10} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, phenyl, phenyl(C_{1-4})alkyl, phenoxy, phenylthio, phenyl(C_{1-4})alkoxy, heteroaryl, heteroaryl(C_{1-4})alkyl, heteroaryloxy or heteroaryl(C_{1-4})alkoxy; wherein any of the immediately foregoing phenyl and heteroaryl moieties are optionally substituted with halo, hydroxy, nitro, $S(O)_kC_{1-4}$ alkyl, $S(O)_2NH_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3; wherein q, k, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43} and R^{44} are as defined in claim 1.

10. A compound as claimed in claim 1, 2, 3, 4, 5, 6, 7, 8 or 9 wherein R^1 is 2,6-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4-dimethoxy-6-hydroxybenzyl, 3-(4-dimethylamino-phenyl)prop-2-enyl, (1-phenyl-2,5-dimethylpyrrol-3-yl)methyl, 2-phenylethyl, 3-phenylpropyl, 3-R/S-phenylbutyl, 3-cyano-3,3-diphenylpropyl, 3-cyano-3-phenylpropyl, 4-(*N*-methylbenzamido)-3-phenylbutyl or 3,3-diphenylpropyl.

11. A pharmaceutical composition which comprises a compound of the formula (I) as claimed in claim 1, or a pharmaceutically acceptable salt thereof or solvate thereof, and a pharmaceutically acceptable adjuvant, diluent or carrier.

12. A compound of the formula (I), or a pharmaceutically acceptable salt thereof or solvate thereof, for use as a medicament.

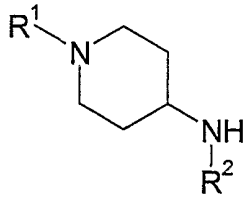
13. A compound of formula (I), or a pharmaceutically acceptable salt thereof or solvate thereof, in the manufacture of a medicament for use in therapy.

14. A compound of formula (I), or a pharmaceutically acceptable salt thereof or solvate thereof, in the manufacture of a medicament for use in modulating CCR5 receptor activity in a warm blooded animal.

15. A method of treating a patient comprising administering a compound of formula (I) as claimed in claim 1, or a pharmaceutically acceptable salt thereof or solvate thereof, or a composition as claimed in claim 11.

16. A process for the preparation of a compound of formula (I) as claimed in claim 1 comprising:

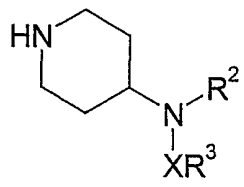
a. reductively aminating a compound of formula (II):



(II)

with an aldehyde R^3CHO; or

b. where R^1 is optionally substituted alkyl, reacting a compound of formula (III):



(III)

with an alkyl halide, in the presence of a base.

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tional application No.
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A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 211/58, C07D 401/06, C07D 401/12, C07D 405/06, C07D 405/12, C07D 409/12, , C07D 411/12, C07D 413/12, C07D 413/14, A61K 31/4468, A61K 31/4523, A61P 1/00, A61P 11/00, A61P 17/00, A61P 19/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	EP 1013276 A1 (PFIZER LIMITED), 28 June 2000 (28.06.00) --	1-16
P,X	WO 0114333 A1 (ASTRAZENECA UK LIMITED), 1 March 2001 (01.03.01) --	1-16
P,X	WO 0076973 A1 (MERCK & CO. INC.), 21 December 2000 (21.12.00) --	1-16
P,X	WO 0076513 A1 (MERCK & CO. INC.), 21 December 2000 (21.12.00) --	1-16

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 Sept 2001	19 -09- 2001
Name and mailing address of the ISA Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Nebil Gecer/BS Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 9925686 A1 (TEIJIN LIMITED), 27 May 1999 (27.05.99)	1-16
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X	WO 9904794 A1 (MERCK & CO. INC.), 4 February 1999 (04.02.99)	1-16
	--	
X	EP 0643057 A1 (BRISTOL-MYERS SQUIBB COMPANY), 15 March 1995 (15.03.95), see examples	1-7,9-16
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X	EP 0625507 A2 (NISSHIN FLOUR MILLING CO. LTD.), 23 November 1994 (23.11.94), see examples	1-7,11-16
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X	EP 0445862 A2 (JANSSEN PHARMACEUTICA N.V.), 11 Sept 1991 (11.09.91), see e.g. tables 2 and 3, pages 27-35	1-7,11-16
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X	EP 0354568 A2 (JAPAN TOBACCO INC.), 14 February 1990 (14.02.90), see claim 2	1-7,10-16
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STN International, file CAPLUS, CAPLUS accession no. 1990:558675, document no. 113:158675, Yoshitomi Pharmaceutical industries, Ltd: "Dihydroxycinnamic acid amide derivatives and their pharmaceutical compositions for enhancement of nerve growth factor (NGF) production & JP,A2,02104568,19900417 --	1-7,10-16
X	STN International, file CAPLUS, CAPLUS accession no. 1978:22640, document no. 88:22640, Yoshitomi Pharmaceutical Industries, LTD: "Urea and thiourea derivatives"& JP,A2,52085174,19770715 --	1-7,11-16
P,X	J. Med. Chem., Volume 44, 2001, Akira Naya et al, "Design, Synthesis, and Discovery of a Novel CCRI Antagonist" page 1429 - page 1435 --	1-16
X	Synthesis, Volume, May 1997, R. Michael Lawrence et al, "Automated Synthesis and Purification of Amides: Exploitation of Automated Solid Phase Extraction in Organic Synthesis", page 553 - page 558, see table 1, page 554 --	1-7,10
X	J. Comb. Chem., Volume 2, 2000, Warren S. Wade et al, "Application of Base Cleavable Safety Catch Linkers to Solid Phase Library Production", page 266 - page 275, see page 269, scheme 3 and table 2, compounds 32 a-m --	1-8
X	J. Med. Chem., Volume 23, 1980, J.L. Archibald et al, "Antihypertensive Ureidopiperidines", page 857 - page 861, see particularly tables I and II --	1-8,11-16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/01053

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Journal of Neuroimmunology, Volume 47, 1993, George B. Stefano et al, "Human neutrophil and macrophage chemokinesis induced by cardiopulmonary bypass: Loss of DAME and IL-1 chemotaxis", page 189 - page 198, see compound named fentanyl -- --------	1-7,10-16

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Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 15
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet*

2. ☒ Claims Nos.: 1-16
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

see next sheet**

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

*
Claim 15 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds/compositions.

**

Present claims 1-16 relate to an extremely large number of possible compounds. In fact, the claims contains so many options, variables and possible permutations that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible.

Consequently, the search has mainly been carried out for those parts of the application which appears to be clear and concise, namely the exemplified compounds of Tables I, II, III and IV and closely related homologous compounds.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established will not be the subject of an international preliminary examination (Rule 66.1 (e) PCT). This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/08/01

International application No.
PCT/SE 01/01053

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		JP 2000212159 A	02/08/00
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		WO 0039125 A	06/07/00
		GB 9922702 D	00/00/00
WO 0114333 A1	01/03/01	AU 6461600 A	19/03/01
		SE 9902987 D	00/00/00
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WO 0076513 A1	21/12/00	AU 5473800 A	02/01/01
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		TR 200001399 T	00/00/00
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		EP 0971887 A	19/01/00
		EP 1003514 A	31/05/00
		GB 9800958 D	00/00/00
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INTERNATIONAL SEARCH REPORT

Information on patent family members

02/08/01

International application No.
PCT/SE 01/01053

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